EXHIBIT 500

Digitek Product Litigation Expert Witness Report
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1. Purpose

This report is a thorough, detailed and independent review of the facts related to Digitek Product Litigation. In particular, this review was specifically conducted to determine if Amide Pharmaceutical, Inc. (which later became Actavis Totowa, LLC and referred to as Amide/Actavis within this report) demonstrated a systemic failure to implement quality systems which in turn created a high likelihood that adulterated drug product made it to the marketplace.

2. Background and Qualifications

Summary

My name is Dr. David M. Bliesner, Ph.D. I am President of Delphi Analytical Services, Inc. which is a private consulting firm that has been in business since February 1999. Delphi Analytical Service's mission is to improve our clients' level of compliance with the Current Good Manufacturing Practices (CGMPs) and Quality System Regulations (QSRs) by providing consulting services, instructional technology, instruction, and compliance products. Delphi's core competencies include (1) Quality Assurance auditing and process improvement (2) Developing and implementing corrective action plans especially related to FDA regulatory action including Consent Decrees (3) Instruction in CGMPs (4) Video-based learning software and online educational product development via our patent-pending process. Our clients include companies from the "top ten" list of pharmaceutical, biopharmaceutical, medical device, and contract analytical industries as well as smaller firms. I am also an Associate Professor at Saint Leo University, Saint Leo, Florida.

Education and Work History

I am a graduate of the United States Naval Academy Class of 1983 where I earned a bachelor's degree in chemistry which is certified by the American Chemical Society. I have a Ph.D. in Analytical Chemistry for the University of Vermont. My dissertation is titled "Chromatographic and Nuclear Magnetic Resonance Studies of Reversed Phase Liquid Chromatographic Interphases". I finished my Ph.D. studies in just under four years. I continue to be actively involved in education and training particularly in the field of CGMPs. I teach CGMPs and other compliance and related courses at client sites and international conferences. I develop and present new course materials and have produced video-based online instruction which I offer for sale via the internet. I am a published author of technical and compliance related articles and texts. I am sole

author of the book titled "Establishing a CGMP Laboratory Audit System: A Practical Guide and "Validating Chromatographic Methods: A Practical Guide" both published by Wiley-Interscience, John Wiley and Sons, Publishers. I am a member of the American Chemical Society (ACS-22 years) and the American Association of Pharmaceutical Sciences (AAPS-10 years). To keep current in my field I frequent the FDA website, purchase and read text published by the American Society of Quality (AQS), the International Society for Pharmaceutical Engineering (ISPE) and Wiley-Interscience. I periodically attend conferences held by the AAPS and attend and teach at the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy (PittCon) almost on a yearly basis. In addition, I have frequent conversations with clients, colleagues, and former clients with respect to their current efforts to implement CGMPs. I have a unique and diverse work history which gives me a unique perspective. This work experience includes serving as a Unit Commander in the United States Marine Corps prior to my entrance into graduate school. Following graduate school I served in a wide variety of positions within very large and smaller firms in the Pharmaceutical (both innovator and generic), Contract Analytical and related industries.

Pertinent Skills Sets Applicable to this Case

Some specific skills, which relate directly to this current project include:

- A comprehensive understanding or working knowledge of most major analytical techniques including HPLC, GC, TLC, FTIR, UV/Visible spectroscopy, wet chemical analyses, particle size analysis, raw material and finished product release testing
- Formulation development and excipient compatibility studies
- Dosage form development including tablets, capsules, oral solutions, and transdermal patches
- Analytical methods development and validation
- Support of process validation studies
- Designing, building, staffing and qualifying analytical chemistry laboratories for operation under CGMPs
- Quality Control (QC) laboratory operations and leadership
- Creation and operation of document control systems including writing, reviewing, revising and controlling standard operating procedures (SOPs)
- Collecting, recording, reviewing, storing and archiving observations and data
- Conducting Out of Specification (OOS) and laboratory error investigations
- Serving on cross-system quality review teams

Consulting Experience

In addition to the skills listed above, my consulting duties have involved serving as part of a third party expert consultant contingent mandated by FDA for

companies operating under consent decrees. This experience involved auditing, capturing deficiencies, and reporting final results. In addition, I also served as a corrective action verifier to certify that the companies have implemented valid systems-based corrective actions, that personnel have been trained on these actions, that the corrective actions are working and that there is data to support the verification. Some of my more recent assignments have included assisting a large Medical Device firm better understand and comply with the CGMPs and Medical Device Quality System Regulations (QSR) as they relate to submission of marketing applications for drug-medical device combinations. I am also helping a client establish a practical and efficient Out of Specification (OOS) investigation system, and helping another client by reviewing manufacturing and laboratory investigation reports.

Expert Witness Experience

This is my first expertise witness assignment.

3. Overview of the Current Good Manufacturing Practice Regulations and Quality Systems

The Essence of the Current Good Manufacturing Practice Regulations

The Current Good Manufacturing Practice Regulations commonly referred to as GMP, is the law. Codified in 21 Code of Federal Regulations (CFR) Parts 210 and 211. The GMPs were enacted by Congress and they are the regulations that "….contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess." (Reference: http://www.access.gpo.gov/nara/cfr/waisidx_10/21cfrv4_10.html, http://edocket.access.gpo.gov/cfr_2009/aprqtr/21cfr210.1.htm).

In my experience, the purpose of the GMPs is to lay out the *minimum* standards required in order to insure drugs are safe, effective and have the properties promised by the manufacturer. The GMPs are not a "how to manual", but a starting point for manufacturers to produce safe and effective products. In addition, GMPs are most often referred to as Current Good Manufacturing Practices, cGMPs or CGMPs. The "C" in CGMPs means the best practices in the industry which, is currently being applied today. In my experience, FDA also recognizes industry standards and best practices and expects all manufacturers to operate at that level even if it is not spelled out specifically in the regulations.

When teaching CGMP compliance courses, I instruct my students that the essence of the CGMPs is captured in the following statement:

Compliance with Current Good Manufacturing Practices Means Showing you are in Control of Your Operations

Therefore, if you are not in control of your operations you are not in compliance with the regulations.

Quality Systems: The Best Way to Comply with the CGMPs

Activities found in drug firms are typically organized into six systems. These systems are sets of operations and related activities and they include: (1) The Quality System (2) The Facilities and Equipment System (3) The Materials System (4) The Production System (5) The Packaging and Labeling System and (6) The Laboratory Control System.

Control of all systems helps to ensure the firm will produce drugs that are safe, have the proper identity and strength, and meet the quality and purity characteristics as intended. (Reference: Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm)

A graphical depiction of these six systems is shown below:

Collectively, these six systems are referred to as Quality Systems. Compliance with the CGMPs is typically accomplished by implementing a Quality Systems based approach. Of particular note in this diagram:

- All six systems are integrated and intertwined with each other and do not stand alone
- Every drug product manufactured at a facility is impacted by Quality Systems
- If one of the systems is out of compliance then it impacts all drug products manufactured at the facility
- The Quality System (typically thought of as Quality Assurance) is the overarching system which impacts and encompasses the remaining five systems
- Failure of the Quality System (Quality Assurance) means all products manufactured, tested, packed and held are at risk of being adulterated.

In 2002 FDA began using a Quality Systems based approach in their assessment of drug firms by using Compliance Program Guidance Manual (CPGM) 7356.002 "Drug Manufacturing Inspections" as a guide during inspections. This document exists and is accessible to the public through the FDA website (Reference: http://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograManual/default.htm#drugs). FDA has used this document as a guide to inspect Amide/Actavis facilities since at least 2006 (Reference: See Attachment A18). In my opinion, this document is well known in the industry.

In addition to CPGM 7356.002, FDA also issued a Guidance Document in 2006 titled "Quality Systems Approach to Pharmaceutical Regulations" (Reference: See Attachment A12 and Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm). The intent of this document is to help manufacturers implement modern quality systems to meet the requirements of the CGMPs. The guidance is not intended to place any new expectations on manufacturers or replace the CGMPs, but to assist them in compliance with the law. Where appropriate in this document, correlations between quality systems and the CGMPs are highlighted. In my opinion, this guidance is well known in the industry.

Of particular note, based on my experience, the 2006 Guidance Document for Quality Systems Approach to Pharmaceutical Regulations emphasizes the importance of leadership and management responsibilities in the proper implementation of Quality Systems. Leadership and Management responsibilities per say is not explicitly required in the CGMPs. However, modern robust quality system models call for management to play key roles in the design, implementation and control of the quality system. Therefore, Management Responsibility and Leadership are recognized as crucial and they represent an example of the "C" in CGMPs which are industry best practices. (Reference: See Attachment A22 and Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm).

4. Review of Amide/Actavis Status of Compliance with CGMPs: My Approach

In order to accurately evaluate the status of Amide/Actavis's status of compliance with the CGMPs I took the following approach:

- Assumed Amide/Actavis was a new consulting client needing assistance with respect to determining their level of compliance with the CGMPs
- Performed a "Paper Audit" of the facility to determine past and current status of compliance with respect to the CGMPs. This audit included:

    1. Review of FDA actions including Form 483s, Warning Letters, Complaints and Consent Decrees, and Establishment Inspection Reports (EIRs)
    2. Review of Amide/Actavis responses to these actions
    3. Conducted "Interviews" of key personnel by reviewing records of depositions
    4. Review of Amide/Actavis internal documents, memoranda, standard operating procedures, and e-mails
    5. Review of customer internal documents, memoranda, and e-mails
    6. Review of the Abbreviated New Drug Application (ANDA) for Digitek

- Selected, collated and compiled a key documents list throughout the process
- Selected, collated, compiled an FDA actions list throughout the process
- Selected, collated and compiled a list of facts regarding Digitek tablet manufacturing
- Presented key documents in tabular format
- Presented FDA actions in a tabular format
- Presented facts regarding Digitek tablet manufacturing in list format
- Wrote this report using information extracted from all these documents, tables and lists
- Referred to both document tables and lists as needed

It should be noted that I have reviewed over 8,000 pages of documents in order to generate this report. In addition, should additional information become available for my review I reserve the right to supplement my opinions based on the new information.

References used to make my conclusions are listed in Attachment A: "Selected Reference Documents for Digitek CGMP Compliance Review-Approximate Chronological Order" and Attachment B: "Summary of Some FDA Actions: Amide Pharmaceutical, Inc., Actavis/Amide". In addition, I have compiled a

document called “Some Facts Regarding Digitek Tablet Manufacturing”. It is included below as Attachment C.

5. Summary of Actions Taken by FDA against Amide/Actavis Pharmaceuticals

Amide/Actavis is a company with an extensive 27 year history of non-compliance with the CGMPs. which has led to repeated release of adulterated product to the marketplace.

The following is a summary of actions taken by FDA in an attempt to assist, prompt, cajole, and force Amide/Actavis to comply with the law:

FDA Action		**Number of Occurrences**		**Description**
FDA Form 483		26		First FDA Form 483 issued in 1983 during first FDA site visit; Last Form 483 issued in 2009. Most all Form 483s have numerous observations. (Reference: See Attachment A1, B46)
Warning Letters		6		These Warning Letters highlighted “Significant deviations from the Current Good Manufacturing Practice (cGMP) regulations set forth in Title 21, Code of Federal Regulations, Parts 210, 211, in conjunction with your firm’s manufacture of prescription drug products”. Reference: See example Attachment B32, B33)
Product Recalls		4		1990 Class II: Super or sub potent tablets due to thickness 1995 Class III: Incorrect package insert (a failure of packaging and labeling portion of the CGMPs) 2008 25 April, Class I Digoxin double thick or super potent 2008 1 August, total product recall

FDA Action		Number of Occurrences		Description
				from Actavis Totowa Little Falls , New Jersey Site, 66 products total. (Reference: See Attachment A49, A55, A63)
Consent Decrees		2		First Consent Decree signed in 1992 by Chandu Patel, 23 March 1992. Second Consent Decree signed in 2008 by Sigurdur Oli Olafsson and Douglas Boothe, 23 December 2008. (Reference: See Attachment B6, B45)

It should be noted, in my experience Consent Decrees are not common and mostly occur when a company has shown repeated and persistent non-compliance with the law.

Attachment B gives a more detailed description of the FDA actions summarized above and includes linkages to Plaintiff's Exhibits and FDA sources documents.

6. A Summary of Some Facts Regarding Digitek Tablet Manufacture and the Company's Chronic and Continuing Failures of Compliance with the Current Good Manufacturing Practice Regulations

Manufacturing and related activities for Amide/Actavis took place at three separate locations over the course of over 27 years. These include:

- 101 East Main Street, Little Falls, New Jersey 07424 (Little Falls)
- 990 Riverview Drive, Totowa, New Jersey 07512 (Riverview)
- 4 Taft Road, Totowa, New Jersey 07512 (Taft Road)

The majority of my observations however relate to the Little Falls, New Jersey facility however compliance issues exist at all sites as would be expected by multiple sites lead by the same management.

The following are some historical facts regarding Digitek tablet manufacturing presented in approximate chronological order:

1. Digoxin has been used as a heart drug for over 230 years. Digoxin tablets have been on the market in the United States since 1938. (Reference: See Attachment A69)

2. Digoxin has a narrow therapeutic index which means that a very narrow range of concentration in the bloodstream must be maintained or toxicity or lack of effect can occur. (Reference: See Attachment A69)

3. Difficulty in manufacture of Digoxin tablets has been known for some time and a concern to FDA early on. This fact prompted Congress to pass the Digoxin Regulation in 1974 (21 CFR Part 310.500) which required manufacturers of Digoxin tablets to submit their products to FDA for certification. (Reference: See Attachment A10)

4. June 1995 FDA issues certification to Amide Pharmaceuticals allowing them to manufacturer and sell Digoxin under the Batch Certification Regulation 21 CFR 310.500. (Reference: See Attachment B11)

5. Continued product safety concerns by FDA prompted the repeal of 21 CFR 300.15, thus requiring the submission of an NDA by the product innovator Burroughs-Welcome, which was approved in 1995 with the trade name Lanoxin. (Reference: See Attachment A10)

6. During the same period, Amide executed an extensive year long product development effort to formulate, manufacture and collect data to support submission of an ANDA for Digoxin tablets, thus confirming the concern FDA has with respect to the difficulties associated with manufacturing Digoxin tablets. Amides efforts resulted in at least 40 to 50 experiments before the proper formulation was achieved. (Reference: See Attachment A7)

7. Process validation which was included in the ANDA application for Digoxin tablets occurred in mid-November 1997. Process validation did not include all strengths of the product. Process validation was performed only on 0.250 mg strength tablets. The .250 mg tablet is white and does not contain colorant. The 0.125 mg tablet is green and the 0.500 mg tablet is yellow. (Reference: See Attachment A8)

8. Successful formulation of Digoxin tables required micronization during product manufacture. Micronization is the process of transforming active ingredient and/or excipients into a fine powder. Fine powders led to problems with static electricity during manufacturing especially during the winter months. (Reference: Attachment A7, A34)

9. On 21 February 2001 the Law Firm of McKenna & Cuneo, LLP of Washington DC argued on behalf of Bertek Pharmaceuticals and Amide for revocation of the 1974 Digoxin Regulation (21 CFR Part 310.500) to "…ensure that the marketplace does not include Digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence,

formulation and manufacturing changes that have not been approved by FDA and unproven labeling claims". (Reference: Attachment A10)

10. Amide first experienced difficulties with FDA from 28 July to 9 August 1983 during its first inspection shortly after the Little Falls, New Jersey facility opened. Major findings included:

    a. Stability testing program didn't support 2 year expiration
    b. Control of labels was inadequate
    c. Personnel making unauthorized changes to batch records
    d. Unaccounted loss of material during manufacture of tablets

    (Reference: Attachment B1)

11. From September 1984 to March 1989 (~5 ½ years) FDA inspections of Amide at Little Falls finds repeated, significant violations of the CGMPs. Major findings include:

    a. Insufficient methods validation
    b. Unsound methodology
    c. Inadequate review of data
    d. Improper calibration practices
    e. Poor record keeping
    f. Lack of submission of periodic reports on ANDA products,
    g. Insufficient stability data

    (Reference: Attachment B1, B2)

12. December 1990 Class II recall initiated for variation in tablet size resulting in sub and super potent drug product, demonstrating lack of manufacturing controls since at least this time. (Reference: Attachment B5)

13. First Consent Decree of Injunction signed by between Chandu Patel, President, Amide Pharmaceutical, Inc. and US Justice Department. Specific points FDA required by include:

    a. QA personnel must be adequate in number and have background, education, training, experience or combination therein
    b. QC (laboratory personnel must be adequate in number and have background, education, training, experience or combination therein
    c. All laboratory and analytical procedures shall be validated
    d. Laboratory practices shall reflect actual written SOPs and be followed
    e. Records required by GMPs shall be kept and recorded at the time events occurred
    f. Validations to be reviewed by third party
    g. Laboratory instrument procedures to be reviewed by third party

h. Laboratory analyst shall be trained by third party for each type of instrumentation
i. Manufacturing methods, facilities and controls to be reviewed by a third party
j. All products to be certified by third party
k. Third party to certify to FDA all actions have been taken

(Reference: Attachment B6)

14. From 23 March 1992 until 10 June 2002 Amide is frequently inspected by FDA under terms of the Consent Decree and for ANDA Pre-Approval Inspections. FDA writes numerous Form 483s with multiple observations. FDA denies Amide request to lift the Consent Decree on at least three separate occasions. (Reference: Attachment B6-B10, B13-B19, B21-B23)

15. 10 August 1995 Class III product recall initiated by Amide for incorrect package insert. (Reference: Attachment B12)

16. October 1997, Amide submits ANDA to produce Digoxin tablets using process validation data generated in 1994. (Reference: Attachment A8)

17. Amide receives approval from FDA to manufacture and sell Digoxin Tablets on 23 December 1999. (Reference: Attachment B20)

18. 9 May 2000, Adverse Drug Event for Digoxin reported to Amide: Death Occurs 2.5 hours after taking Digitek. Event not reported to FDA. (Reference: Attachment A9)

19. 29 October to 29 November 2001, FDA inspects Amide and makes the following Form 483 observations:

a. Thin tablets observed by packaging personnel
b. Visual inspection resulted in rejection of 1,600 tablets
c. FDA states no assurance that all short weight/thin tablets were rejected
d. No written rework procedure in place
e. No assurances that all 32 stations of tablet press yields tablets within specification for weight or thickness because only 10 of 32 stations were checked during operational/performance qualification studies and compression start-up.

(Reference: Attachment A11)

20. FDA Form 483 Observation for the 29 October to 29 November 2001 states:

"During the packaging of [redacted] thin tablets were observed by packaging personnel. A portion of the batch (drum 4, 7, 8, & 11) was visually inspected

for the presence of thin tablets, which resulted in approximately 1,600 tablets being rejected and ultimately the rejection of drums 4, 7, 8 and 11. The entire contents of drum 1,2,3,5,6,9 and 10 were packaged. During packaging, the packaging line was run at slower speed so that thin tablets could be observed on the tracks.

- There is no assurance that all short weight/thin tablets were rejected from the batch
- There was no rework procedure written for the tablet inspection of drums
- During operational/performance qualification studies from compression start-up, 10 & 32 stations of the tablet press are checked for weight and thickness. Therefore, there is no assurance that all 32 stations of the tablet press yield tablets within specifications for weight and thickness"

As part of their response to FDA, Jasmine Shah, Director of Regulatory Affairs states:

"In order to handle this type of problem in the future, Amide has purchased tablet sorting equipment that will sort thick/thin tablets. Enclosed is a purchase order copy for the equipment (Attachment 1). Upon receipt of the equipment, an IQ/OQ/PQ will be performed and the equipment will be used if such a situation arises."

(Reference: A11, Plaintiff's Exhibit 236)

21. 10 June 2002, FDA lifts first Consent Decree (Reference: Attachment B23)

22. 8 June 2004 Amide receives complaint from a pharmacist in Bellingham, WA regarding thick Digoxin tablet. Amide confirms double thickness, no definitive root cause found. Compression occurred on tablet presses #67 or #71. Tablet manufacture occurred 6, 7 and 10 November 2003. No chemical testing conducted on product. This is the first instance of double thick Digoxin tablets reported and confirmed in market place. (Reference: Attachment A13, A14)

23. December 2003 Sigurdur Olafsson is made Managing Director of Actavis US. (Reference: p 24, Sigurdur Olafsson deposition 10 February 2010)

24. 16 July 2004 Sigurdur Olafsson begins conducting due diligence review of Amide for potential purchase by Actavis hf. He finds no problems with respect to FDA or compliance with CGMPs. (Reference: Plaintiff's Exhibit 190)

25. Formal due diligence conducted by Actavis for purchase of Amide Pharmaceutical, Inc. from July 2004 to July 2005. According to CEO Sigurdur Olafsson, outside consultants used for detailed due diligence consisting of an operation team and a quality team. No problems with respect to FDA or compliance with CGMPs. (Reference: p 50-52, Sigurdur Olafsson deposition 10 February 2010)

26. Actavis purchases Amide Pharmaceuticals on 27 July 2005. Purchase includes Little Falls Facility (main site), Taft Road Facility and Riverview Facility all within close proximity to one another. Little Falls is the original facility where most of the manufacturing and compliance related difficulties occurred. (Reference: p 24, 225 Divya C. Patel deposition 30 April 2010)

27. 15 May 2006, company named changes from Amide Pharmaceutical, Inc. to Actavis Totowa, LLC following sale to Actavis Group, hf. (Reference: Plaintiff's Exhibit 91)

28. January 2006, Sigurdur Olafsson is made President of Actavis US. (Reference: p 62, Sigurdur Olafsson deposition 10 February 2010)

29. 10 January 2006 to 8 February 2006 FDA inspects Actavis Totowa, Little Falls, New Jersey and writes a Form 483 with 8 observations. Inspection is primarily related to pharmacovilgilence. Specifics include:

    a. Adverse drug experiences not reported to FDA within proper time frame or not reported at all, including Death Associated with Digitek on 9 May 2000 2.5 hours after taking Digitek
    b. No review of literature related ADE for products
    c. No written procedures for ADEs
    d. Failure to investigate consumer complaints including a metal screw found in a bottle of product
    e. Failure to investigate OOS percent yield of bulk material
    f. No process validation
    g. Qualification and start-up procedures in manufacturing is inadequate

    (Reference: Attachment A16)

30. In e-mails from Ashok Nigalaye to Divya Patel and from Ashok to Bharat Patel dated 12 July 2006 and 21 July 2006. Discussion about purchasing new tablet presses which contain tablet weight and thickness controls, including an equipment quote #26943 from DLS Enterprises. (Reference: Plaintiff's Exhibit 258 and 259)

31. 10 July to 10 August 2006, FDA inspects Actavis Totowa, LLC Little Falls, New Jersey. Inspectional coverage includes the Quality System, Laboratory Control System and Material System. FDA's summary statement pronounced:

"A review of the firm's manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented."

A Form 483 was issued with 15 observations which included:

a. 1-The Quality Unit Lacks authority to fully investigate errors that have occurred.
b. 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing
c. 3- The responsibilities and procedures applicable to the quality control unit are not fully followed
d. 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications
e. 5- Input to and output from the computer are not checked for accuracy
f. 6- The suitability of testing methods is not verified under actual conditions of use
g. 7- The written stability testing program is not followed
h. 8- Examination of testing samples is not done to assure that in-process materials conform to specifications
i. 9- Deviations from written procedures and process control procedures are not recorded and justified
j. 10- Master production and control records are deficient in that they do not include complete sampling and procedures
k. 11- Equipment used in the manufacture, processing, packing, or holding of drug products is not of appropriate design to facilitate operations for intended use
l. 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product
m. 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable
n. 14- Written procedures are not followed by receipt and storage of components
o. 15- There was a failure to handle and store components at all times in a manner to prevent contamination

Divya Patel is still the most responsible person on site, Jasmine Shah is still primarily responsible for Quality Assurance and Regulatory Affairs, and Dan Bittler is still primarily responsible for Quality Assurance approval and sign-off. These observations are similar and consistent with what FDA has found since its first observations starting in 1983.

(Reference: Attachment A18)

32. 15 August 2006 FDA issues Warning Letter to Actavis Totowa, LLC Little Falls New Jersey regarding inspection conducted 10 January 2006 to 8 February 2006. (Reference: Attachment A19)

33. 4 January 2007 Mylan Pharmaceuticals, Inc. openly states reservations about continued relationship with Actavis.

    "I believe that we should seriously consider looking at either manufacturing the product here or as an alternate site to Amide"

    (Reference: Attachment A24)

34. 1 February 2007, Warning Letter issues to Divya Patel concerning 10 July to 10 August inspection findings. (Reference: Attachment A25)

35. Actavis annual product review for Digitek 0.25 mg tablets on 3 April 2007 for 1 December 2006 to 31 December 2006 finds the following:

    a. 17 Adverse events were noted including some for
        i. Atrial fibrillation
        ii. Elevated Digoxin level in blood
        iii. Orthostatic hypotension
        iv. "Unknown" potency question
    b. Detail of investigations was limited due to inability to trace product in market to lots produced at plant
    c. One lot, 60319A Final Blend Assay Standard Deviation was 4.5% which was higher than other batches
    d. Some additional Content Uniformity and Dissolution vales were "slightly higher" compared to other batches reviewed.

    (Reference: Attachment A27)

36. Blend uniformity failures for different products are discussed in an e-mail from Wanda Eng to Apurva Patel dated 20 July 2007. In particular, Blend Uniformity failures for Digoxin Tablets manufactured on 17 January 2007 and 12 March 2007 are discussed. One lot was rejected after additional testing and one was released. (Reference: Plaintiff's Exhibit 183)

37. 5 September 2007 to 28 September 2007, FDA inspects Actavis Totowa Little Falls, NJ facility as a follow-up to Warning Letter. It is a general GMP inspection and a pre-approval inspection for one product. Summary of findings include:

    a. An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning failure of one or more

distributed batches of drug to meet the specifications established for it in the application (stability failure)

b. Written stability testing program is not followed (36 month pull not tested for four products
c. Written production and process control procedures are not followed in the execution of production and process control functions (DOP #0033 Investigations of Out of Specification Results and DOI # QC-059 are not followed)

(Reference: Attachment A29)

38. 1 October 2007 internal e-mail indicates Digoxin 0.25 mg is the top product where Adverse Drug Events are associated with death or permanent injury. (Reference: Attachment A30)

39. 30 November 2007, Double thick tablets discovered during manufacturing of Digoxin 0.125 mg tablets. Although initially halted, production continued following only visual inspection. Detailed investigation conducted within a very short period of time. Product is released to market without conclusive evidence of what caused the double thick problem on 5 December 2007. No chemical testing of tablets was conducted. (Reference: Attachment A31, A32)

40. Last quarter 2007 Digoxin Blend failure investigation conducted. Potential causes cited include:

    a. Blend sampling procedures (change over to slugs)
    b. Low humidity/high sampling
    c. API particle size
    d. Batch record problems
    e. Method issues
    f. Product validation
    g. Laboratory testing

    According to company document, relative humidity levels were lower for months of October through April. Dryer conditions may lead to electrostatic attractions which may be the cause for the higher number of blend failures. (Reference: Attachment A34)

41. In an e-mail dated 18 December 2007, Richard Dowling states to Bharat Patel:

    "As part of the corrective action for investigation number 07-093 for Digoxin double tablets, I am going to state that we will buy a complete set of lowers and dies for both strengths of Digoxin that will be dedicated and not used for any other products. It is possible the tablet stuck to the punch and was double compressed".

(Reference: Plaintiff's Exhibit 97)

42. From 18 March to 20 May 2008 FDA conducted an inspection of the Actavis Totowa new Riverside facility located at 990 Riverview Drive, Totowa, New Jersey. According to the FDA:

"This inspection was limited to coverage of the Quality System due to significant cGMP deficiencies including but not limited to out of specification in-process, finished product and stability results for more than [redacted] prescription pharmaceutical products; release of Digoxin Tablets 0.125 mg, lot# 70924A2, following visual inspection of the [redacted] to remove "double thick" tablets; failure of the Quality Unit to reject products not meeting specifications, to complete Quality Assurance investigations, to expand investigations to other lots and products, to file NDA Field Alerts within timeframes, and to respond to out of specification products on the marketplace. Analytical methods requiring remediation remained in use and approximately [redacted] prescription drug products had no analytical evaluations of impurities on stability. Written procedures were not followed and changes with potential product quality impact were not all reviewed and approved by the Quality Unit. No market action was taken by the Quality Unit for any products on the market at the initiation of the inspection of the inspection despite confirmed out of specification, in-process, finished product and stability results. During the inspection, commitments to recall products were initiated based on inspectional findings. No comprehensive risk assessment or quality evaluation for all products on the market was conducted by the firm's Quality Unit prior to completion of the inspection. No additional systems were covered following the documented Quality System failure."

"Commitments to recall finished products from the marketplace were initiated on 4/09/08 and continued throughout the inspection for such products as Digoxin Tablets, Pentazocine and Nalaxone Hydrochloride Tablets, Carisoprodol/Aspirn/Codeine Phosphate Tablets, Hydrocodone Bitartrate and Homatropine Methlybromide Tablets and Mult-Bets pediatric prescription vitamins. However, there is no assurance of the strength, quality and purity of the approximately [redacted] of other products that remain on the market, all lots remaining in the two distribution centers, and the in-process products that remain at the firm's Little Falls, NJ and Totowa NJ locations. The products were manufactured, tested and released by the same Quality System".

(Reference: Attachment A37)

43. Actavis issues urgent recall notice to valued customers stating:

"This recall notice has been initiated due to overweight tablets."

(Reference: Attachment A35)

44. 25 April 2008 FDA and Actavis announce recall on all Digitek Tablets on the market. (Reference: Attachment B41)

45. On June 11 2008 Sigurdur Olafsson, now Deputy CEO, Actavis Group, CEO Actavis, Inc. issued response to FDA Form 483's generated during the 8 March to 20 May 2008 FDA inspection. He acknowledges most of the observations, but disagrees when he does not believe them to be correct. The following statement best captures his sentiment:

    "It is quite fair to say, as we related to our April 2008 letter, that Actavis Totowa prides itself in maintenance of cGMP compliance by virtue of comprehensive and robust quality systems. Thus we were surprised and chagrined, as the last inspection developed, by our failure to have secured the compliance we had sought and committed to establish for Actavis Totowa."

    (Reference: Attachment A61)

46. UDL Internal Investigation Record from March 2008 indicates "…one complaint for Digitek 125 mcg (#08-038) reported that the customer observed that the tablets appear smaller than usual and that her heart started racing". This observation was made in March before any recall announcement. (Reference: Attachment A36)

47. Actavis Investigation #08-060 for Digoxin Tablets 0.125 mg Lot # 80228A1, 1 April 2008. Overweight tablets were found during packaging. Preliminary investigation showed a 5000 count bottle had 17 out of 30 tablets above 120 mg. Put on hold pending QA investigation. (Reference: Attachment A39)

48. Actavis contracts Health Hazard Evaluation which is issued 18 April 2008. Conclusions:

    "Double thick tablets could lead to digitalis toxicity; Can result in death. Thin tablets may cause congestive heart failure and arrhythmia."

    (Reference: Attachment A40)

49. Mylan acknowledges Pharmacist identifying double thick products in market place (Reference: Attachment A58)

50. Actavis begins receiving a substantial number of complaints regarding Digitek (Reference: Attachment A59)

51. The management team responsible for all Operations, Administration and Quality at Amide was essentially the same for Amide since 1989 until 2008. These individuals include:

a. Chandu Patel-President (~1984 to April 2003, Father of Divya Patel died, referenced within Divya C. Patel deposition 30 April 2010)
b. Divya Patel- President (1995 to April 2008, took over as President when father died in April 2003, reference deposition 30 April 2010)
c. Ashok Nigayale- R&D (June 1993 to January 2008, reference deposition 31 March 2010)
d. Jasmine Shah- Quality and Regulatory Affairs (1988 to August 2008 reference deposition 26 March 2010)
e. Dan Bitler- Quality Assurance (1995 to 23 May 2008 reference deposition 22 January 2010)

52. Ashok Nigalaye leaves company January 2008 (Reference: p. 29 deposition 31 March 2010)

53. Divya Patel leaves company April 2008 (Reference: p. 190 deposition of Divya Patel)

54. 27 April 2008 Mylan Chuck Koon in an e-mail to Hal Korman expresses concerns about Actavis problems with compliance being know "Well over a year ago." Also talks about how to get out of 10 year contract. (Reference: Attachment A56)

55. Sigurdur Oli Olafsson and Mark Keatley e-mail exchange on 2 May 2008, begins discussion of financial impact of problems associated with Digoxin production at Little Falls. Points include:

    a. What is FY 2008 revenue and gross margin for product?
    b. Any deaths or injuries alleged against us?
    c. Are we covered by insurance vs. product/process liability and Mylan liability?
    d. Estimated recall cost only for this product
    e. Need Digitek answers asap

    (Reference: Attachment A50)

56. Jeffrey Rope and Grudrun Eyjolfsdottir e-mail exchange on 3 May 2008 communicates equipment upgrades and concerns related to Digitek production which include:

    a. Have recommended purchase of 3-4 new PTK [tablet] presses with compaction force weight control and automatic reject.
    b. Digoxin presses will be fitted with Kramer de-duster to protect operators from Digoxin tablet dust during packaging.
    c. "In my view it is totally unacceptable that our people cannot read English operating procedures and batch records."

Jeffrey Rope confirms manufacturing people cannot read English and therefore cannot read operating procedures and batch records.

(Reference: Attachment A51)

57. In an e-mail dated 6 May 2008 from Mike Adams, Executive Director QA Compliance Mylan Pharmaceuticals to a large number of staff members, the following points were made with respect to the status of Digitek recall:

    a. "Actavis is setting up a process for consumers to obtain a blood test (through Quest)"
    b. "Actavis has addressed over 2,500 medical questions since April 25 2008"
    c. Total call volume to Stericycle since recall notice 128,768

    (Reference: Attachment A59)

58. Actavis indicates plan to purchase new tableting equipment with weight controls (Reference: Plaintiff's Exhibit 140)

59. Dan Bitler leaves company 23 May 2008 (Reference: p. 16 deposition 22 January 2010)

60. Jasmine Shah leaves company August 2008 (Reference: p.8 deposition 26 March 2010)

61. 1 August 2008 Actavis and FDA announce voluntary recall of all products manufactured at Little Fall, New Jersey facility. (Reference: Attachment B43)

62. 14 November 2008 Complaint for Permanent Injunction United States of America vs. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe

    (Reference: Attachment B44)

63. 23 December 2008 Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe.

    (Reference: Attachment B45)

Please see Attachment C for a tabulated listing of these findings.

7. <u>Root Causes for Amide Pharmaceuticals and Actavis Failure to Comply with the CGMPs Which Led to Release of Adulterated Product to Market</u>

Following a thorough analysis of references cited in Attachments A and B the following root causes can be attributed to Amide/Actavis repeated failure to comply with the CGMPs which resulted in adulterated product to reach the market:

- **Lack of Leadership and Management Controls at All Levels Within the Organization**

  (Reference: Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm specifically pages 8-12)

- **A Lack of Quality Assurance Oversight**

  (Reference: 21 CFR Sec. 211.22 (a))

- **A Poor Document Control System and Poor Documentation Practices**

  (Reference: 21 CFR Sec. 211.22 (b))

- **Unqualified Personnel Serving in Various Positions of Management and in General Employment**

  (Reference: 21 CFR Sec. 211.25)

- **Lack of a Proper Training and Qualification System for Employees at All Levels**

  (Reference: Reference: 21 CFR Sec. 211.25)

8. Conclusions

The findings presented above are based upon existing, available documentation. From the review of these documents it is apparent that Amide/Actavis is a company with an extensive 27 year history of non-compliance with the CGMPs. It is my opinion to a reasonable degree of certainty that the systemic failure to implement quality systems and to comply with the regulations resulted in adulterated drug product making it to the marketplace.

9. References

See Attachments A through D below.

/s/ David M. Bliesner
Dr. David M. Bliesner, Ph.D.

Attachment A:

Selected Reference Documents for Digitek CGMP Compliance Review-Approximate Chronological Order

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A1		Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Conducted 28 July to 9 August 1983	9 August 1983	Available through www.foiservices.com	Form 483 is from initial inspection of Little Falls, New Jersey facility shortly after it was founded on 1 May 1983. Form 483 issued containing four observations. Specific statements of non-compliance with CGMPs include: • Stability testing program doesn't support 2 year labeling • Label control system is inadequate • Unauthorized changes in batch records with no change in the master formula. • Loss of tablet cores not reconciled at completion of manufacturing
A2		Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Conducted 5 to 20 December 1989 and 2 to 15	For 5 to 20 December 1989 and 2 to 15 February 1990	Available through www.foiservices.com	FDA Summary of Findings states: "Inspection of this generic drug manufacturer was conducted to assess the firm's compliance with a voluntary agreement dated 4/20/89 under assignment #5260 (Exhibit 3A). Four DQRS reports, #77989,

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		February 1990	inspection. Document Created after 15 February 1990		78686, 78013, and 79853, were covered under assignment #5672 (Exhibit 38). Also covered were assignment #5708, a GMP statutory obligation inspection, and assignment #6253 (Exhibit 3C), an HFD-341 request for a special investigation into the firm's compliance with the reporting requirements of 21 CFR 314.SQ(c)(2). Previous inspection of 3/26/89 et al was a follow-up to a violative inspection and found continued serious deviations. An injunction was recommended, and the voluntary agreement ensued. Current inspection found many previous deviations still existing in the laboratory including insufficient validation, unsound methodology, inadequate review of data, improper calibration practices, and poor record keeping. Deviations in other areas include the lack of submission of periodic reports on ANDA products, insufficient stability data for hydralazine HCI, the reuse of parchment paper for drying separate batches of product, and inadequate control of the incubator."
A3		Consent Decree of Injunction, Amide Pharmaceuticals, Inc. a Corporation and Chandu Patel, an Individual. Civil Action Number 92-513 Consent Decree of Injunction	23 March 1992	Provided by Miller Law Firm	This is a consent decree entered into by founder of Amide Pharmaceuticals and Department of Justice in March 1992. It is the result of continued failure to comply with the CGMPs even after efforts on the part of FDA to help Amide improve their compliance. Previous efforts included issuance of a memorandum of understanding which included a plan for improvement.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					Specific statements of non-compliance with CGMPs in the Decree include: • QA personnel inadequate in number and have background, education, training, experience or combination therein • QC laboratory personnel inadequate in number and don't have background, education, training, experience or combination therein • Not all laboratory and analytical procedures validated • Laboratory practices don't reflect actual written SOPs and be followed • Records required by GMPs not kept and recorded at the time events occurred • Validations need to be reviewed by third party • Laboratory instrument procedures need to be reviewed by third party • Laboratory analyst need be trained by third party for each type of instrumentation • Manufacturing methods, facilities and controls to be need to be reviewed by a third party • All products need to be certified by third party • Data not properly recorded
A4		Establishment Inspection Report (EIR) for FDA	16 March 1994	Available through www.foiservices.com	This report was issued following an inspection conducted by FDA starting 16 March 1994. This

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Inspection of Amide Pharmaceuticals, Inc. Inspection Conducted 16 March 1994			inspection was a follow up to a previous inspection conducted 9 March 2003 which revealed the firm had not corrected some of the deficiencies previously cited and had not adhered to the terms of the consent decree. This particular inspection cited the following continuing CGMP issues: • Failure to conduct retrospective or prospective process validation as committed to under consent decree nor demonstrated understanding of their importance • Methods not properly validated • Changes to methods not justified or validated • Cleaning validation studies not performed • SOPs were not consistently followed • QA approval not always gained before manufacturing process is initiated • Admission by Chandu Patel on large errors made by QA personnel • Blending process changes in the middle of validation batch production without investigation as to potential impact • Lack of control of contractors performing manufacturing steps • Loss of active ingredient during drying and final blending/compression without concern or explanation

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					• Products manufactured during validation lots without pre-determined acceptance specifications • Manufacturing investigations not complete and not appropriately documented • Black foreign material in final blend and finished product not adequately investigated This EIR is very similar to the final EIR issued in 2006
A5		Response by Jasmine Shah to Form 483 inspection observation by FDA: Poor Laboratory Practices for Digoxin Dissolution Testing	17 March 1995	Available through www.foiservices.com	Letter by Director Regulatory Affairs to FDA District Office in Newark New Jersey addresses FDA 483 observation for inspection conducted on 16 March 1995 which stated "Poor laboratory practices were observed in the sampling of solutions from the dissolution apparatus during testing of Digoxin tablets batch 5069A and the resample of the batch." This is the first instance of Digoxin linked with FDA findings discovered in my review.
A6		Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceuticals, Inc. Inspection Conducted November 1997	1 December 1997	Available through www.foiservices.com	Inspection related to 1992 Consent Decree follow up-still significant GMP issues related to: • Incomplete impurity profile testing on finished drug product • Failure to identify all known starting impurities • Inadequate cleaning validation • Failure to have SOPs for a wide variety of tasks

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					including water sampling, validation data for hardness testing, HPLC data audit trails, adequate calibration and maintenance programs, etc. • No stability data to support expiration dating for in-house standards • No environmental monitoring of warehouses • Laboratory analysts testing samples into compliance and not following OOS SOP • Inadequate alternate manufacturing procedures • No timeline for complete manufacturing investigations • Can track rejected product to destruction manifests. •
A7		Deposition of Ashok Nigalaye, Ph.D.	31 March 2010 containing comments with respect to work done in 1999 or sooner	Made available through internet portal	Deposition is in regard to Digitek product liability suit. The following points are extracted from Dr. Nigalaye's testimony: • Dr. Nigalaye was the person who developed the Digitek formulation p.40 • He testifies that Digoxin has a narrow therapeutic index (e.g. have to control the level in the bloodstream) p.42 • He testified that there have been historical problems with formulating Digoxin in the industry at large. Consistent problems have existed in the past with respect to manufacture of Digoxin products. P.50-52

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					• Dr. Nigalaye testified that "…..we conducted at least 40 to 50 experiments before we came about this formulation" p. 96 • It took about a year to derive the current formulation of Digitek p.98 • He claims they have made "billons and billons without market complaints". P.66 (NOTE: There is evidence to the contrary as per discovery of thick tablet by a pharmacist in 2004) • Dr. Nigalaye makes the statement "We had excellent results. We never failed for quality any batch in the lab." P.115 NOTE: This is not true. There have been blend uniformity failures such as the "double think lot in November 2007" some of which were rejected for problems with blend uniformity. • He testifies that a pharmacist would notice "….twice as thick as a normal tablet" p.118
A8		ANDA 40-282	December 1999	Made available through internet portal	The following points have been extracted from the Digitek ANDA: • Process validation occurred on 17 November 1994, five years before approval of ANDA • Process validation was performed on only the 0.250 mg dosage strength • The 0.250 mg strength does not have colorant. Colors for the products are as follows:

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					o 01.25 mg is green o 0.250 mg is white o 0.50 mg is yellow • Product is an immediate release dosage form as shown by PK profiles • Product is not granulated by mixed during manufacturing
A9		Adverse Event Not Reported to FDA (Included with Form 483 Observation Dated 8 March 2006)	Date of Event 9 May 2000 (Discovered by FDA 8 March 2006)	Within ACTAV00002891	Death in 2.5 hours after ingestion of first tablet.
A10		Comment to Docket Nos. 00N-169 and 00N-1610; Digoxin Products for Oral Use; Revocation of Conditions for Marketing and Reaffirmation of New Drug Status	21 February 2001	Plaintiff's Exhibit 232	On 21 February 2001 the Law Firm of McKenna & Cuneo, LLP of Washington DC argued on behalf of Bertek Pharmaceuticals and Amide for revocation of the 1974 Digoxin Regulation (21 CFR Part 310.500) to "…ensure that the marketplace does not include Digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence, formulation and manufacturing changes that have not been approved by FDA and unproven labeling claims". NOTE: Unapproved manufacturing changes are one of the consistent delinquencies reported by FDA of Amide.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A11		FDA Form 483 Observation from Inspection spanning Date 29 October to 29 November 2001 And Response by Jasmine Shah, Director Regulatory Affairs (Thin Tablets)	29 November 2001	Plaintiff's Exhibit 236	FDA observed the following: • Thin tablets observed by packaging personnel • Visual inspection resulted in rejection of 1,600 tablets • Packaging occurred at lower speed to detect additional thin tablets • FDA states no assurance that all short weight/thin tablets were rejected • No written rework procedure in place • No assurances that all 32 stations of tablet press yields tablets within specification for weight or thickness because only 10 of 32 stations were checked during operational/performance qualification studies and compression start-up. In response to FDA Jasmine Shah states: • Visual investigation was conducted • Stated thin green tablets would be easy to identify • As a precaution all drums were rejected • Conveyed to FDA that Amide purchased tablet sorting equipment (purchase order attached) • Rework procedure will be created NOTE: No indication of sorting equipment in place during future operations.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A12		Compliance Program Guidance Manual (CPGM 7356.002 titled "Drug Manufacturing Inspections"	1 February 2002	www.fda.gov	Internal FDA document which delineates how FDA employees are to inspection drug manufacturing facilities using Quality Systems Based approach. Draft implementation occurred in 2000 formal acceptance occurred in 2002.
A13		RE: Digoxin Tablets 0.25 mg Amide Complaint # C04-016 Mylan Complaint # 2004S100417	8 June 2004	Plaintiff's Exhibit 241	Letter to Amin Nanji, Rite Aide Pharmacy #5238 220 36th Street Bellingham, WA 98222. In reference to inquiry regarding thick Digoxin Tablet. Please return sample for investigation, letter.
A14		Amide Pharmaceutical, Inc. Investigation Final Report for Digoxin Tablet, 0.25 mg Control No. 3611A Investigation No. 04-003	9 July 2004	Plaintiff's Exhibit 128	Investigation Summary on thick Digoxin tablet: • 5.71 mm thick o Specifications are 2.7 mm – 3.7 mm • Weight 0.272 grams o Specifications 0.114 – 0126 • Definitive cause was not identified, guesses put forth • Compression occurred on machines #67 and #71 • Compression occurred 6,7 and 10 November 2003
A15		Amide Pharmaceutical, Inc. Investigation Final Report for Digoxin Tablet, 0.25 mg Control No. 3611A Investigation No. 04-003:	13 July 2004	Plaintiff's Exhibit 242	Conclusions with respect to thick tablet investigation: • Tablet was thicker than normal • Tablet may have been produced at setup of compression machine

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Final Letter Mr. Amin Nanji Pharmacist			• Isolated incident NOTE: No chemical testing performed to determine potency
A16		FDA Form 483 for Inspection Held 10 January to 8 February 2006	8 February 2006	ACTAV000028901	FDA reported the following in 8 observations: • Adverse drug experiences not reported to FDA within proper time frame or not reported at all, including Death Associated with Digitek on 9 May 2000 2.5 hours after taking Digitek • No review of literature related ADE for products • No written procedures for ADEs • Failure to investigate consumer complaints including a metal screw found in a bottle of product by a patient. • Failure to investigate OOS percent yield of bulk material • No process validation • Qualification and start-up procedures in manufacturing is inadequate
A17		Amide Pharmaceutical, Inc. Company Response by Jasmine Shah, Vice President of Regulatory Affairs and Quality Compliance to FDA	28 February 2006	Plaintiff's Exhibit 230	Amide acknowledges deficiencies in all cases and pledges to implement appropriate corrective actions including review of documentation, reporting results to FDA all revisions of SOPs as appropriate. States:

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Form 483 for Inspection Held 10 January to 8 February 2006, Little Falls, NJ			"We have taken the appropriate actions to correct deficiencies and have implemented procedures to preclude their recurrence wherever possible. We have responded to these Inspectional Observations in a prompt and positive manner, and we commit ourselves to a continuing review of all products and procedures to assure compliance with regulations."
A18		Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa LLC Inspection Conducted 10 July to 10 Aug 2006, Little Falls, NJ	After 10 Aug 2006	Plaintiff's Exhibit 90	This report was issued following an inspection conducted by FDA starting from 10 July 2006 to 10 August 2006. This inspection was a general GMP inspection as well as a pre-approval inspection for certain [redacted] products. This inspection was afforded through Compliance Program Guidance Manual CPGM 7356.002: Drug Manufacturing Inspection and 7346.832 Pre-Approval Inspections/Investigations. Inspectional coverage including the Quality, Laboratory Control and Materials System. FDA's overall assessment: • " A review of the firm's manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented". There were 15 Observations cited in the Form 483 which was issued for the inspection. These included:

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					• 1-The Quality Unit lacks authority to fully investigate errors that have occurred. • 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing • 3- The responsibilities and procedures applicable to the quality control unit are not fully followed • 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications • 5- Input to and output from the computer are not checked for accuracy • 6- The suitability of testing methods is not verified under actual conditions of use • 7- The written stability testing program is not followed • 8- Examination of testing samples is not done to assure that in-process materials conform to specifications • 9- Deviations from written procedures and process control procedures are not recorded and justified • 10- Master production and control records are deficient in that they do not include complete sampling and procedures • 11- Equipment used in the manufacture, processing, packing, or holding of drug products is not of

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					appropriate design to facilitate operations for intended use • 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product • 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable • 14- Written procedures are not followed by receipt and storage of components • 15- There was a failure to handle and store components at all times in a manner to prevent contamination Divya Patel is often cited as the most responsible person at the Little Falls Facility.
A19		Warning Letter 06-NWJ-15 to Divya Patel, President Actavis Totowa, LLC Little Falls New Jersey	15 August 2006	Plaintiff's Exhibit 229	This Warning Letter 06-NWJ-15 was issued following a 10 January to 10 February 2006 Inspection of the Little Falls New Jersey site. The following compliance issues were raised by FDA: • Failure to submit six potentially serious and unexpected adverse events dating back to 1999 for products such as Digoxin that were not reported to

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					FDA • Serious and unexpected ADE reports were not promptly investigated • Failed to adequately review ADE information as required by law • Never filed periodic safety report as required by law • Procedures for surveillance, receipt, evaluation, and reporting of adverse events have not been submitted as required by law.
A20		Response to Warning Letter 06-NWJ-15 by Divya Patel, President Amide Pharmaceutical, Inc. Little Falls New Jersey	6 September 2006	ACTAV000028929	Response states "After reviewing our responses to the form FDA 483 presented to us on February 8 2006 we must acknowledge that we did not provide a comprehensive evaluation of how Amide has administered its Adverse Drug Experience ("ADE") program from 1999 into February or a full description of the changes made to assure future compliance."
A21		Actavis Totowa, LLC Response to FDA Form 483 Observations as a Result Inspection of Amide Pharmaceuticals, Inc. Inspection Conducted 10 July to 10 Aug 2006 Little Falls, NJ	29 August 2006	ACTAV000511447	Companies response to Form 483 Observations is as follows: • 1-The Quality Unit lacks authority to fully investigate errors that have occurred. **Amide disagrees with FDA, however agrees with others and "….that some observations made in this inspection indicate that the quality unit has failed**

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					to assure that all systems, for example, laboratory documentation and preventive maintenance are administered optimally". However, Amide feels that "… the bottom line is that the systems have been and are sufficient to assure product quality". • 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing. **Modified DOI, analyst re-trained on modified procedures and on laboratory documentation in general. Company states "We shall be attentive to assuring this instruction is observed". Semi-annual audits of laboratory notebooks to conduct to evaluate conformance with CGMPs.** • 3- The responsibilities and procedures applicable to the quality control unit are not fully followed. **Tacit agreement to many aspects with some push back on specifics. New SOPs created and personnel trained.** • 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications. **Reported consultant recommended the QC Director implementing that laboratory errors be more extensively documented.** • 5- Input to and output from the computer are not

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					checked for accuracy. **Observation recognized as correct.** • 6- The suitability of testing methods is not verified under actual conditions of use. **Will perform recovery studies for all products missing recovery.** • 7- The written stability testing program is not followed. **Disagrees with observation and provided data to support.** • 8- Examination of testing samples is not done to assure that in-process materials conform to specifications. **Observations are correct. Training conducted to address.** • 9- Deviations from written procedures and process control procedures are not recorded and justified. **Observation is correct. Revised procedures to ensure that unusual observations are documented in the data sheet in the batch record. All personnel receive new training.** • 10- Master production and control records are deficient in that they do not include complete sampling and procedures. **Observation essentially correct. Revised procedures to ensure all events, decisions, and observations bearing on product quality are documented in the data sheet and elsewhere on the batch record.** • 11- Equipment used in the manufacture, processing,

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					packing, or holding of drug products is not of appropriate design to facilitate operations for intended use. **Agree to incomplete qualification of equipment (Tablet press Stokes BB2 Equipment ID # 70) Committed to review all re-qualification reports and will write discrepancy report for deviations. NOTE: This is one of two presses involved in Digoxin Double Thick Tablet Production** • 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product. **Duct tape removed; personnel trained not to make modifications. Procedures written or re-written as needed.** • 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable. **Agree with some, not with others; reviewing, revising and training as necessary.** • 14- Written procedures are not followed by receipt and storage of components **Agree with some, not with others; reviewing, revising and training as necessary.** • 15- There was a failure to handle and store

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					components at all times in a manner to prevent contamination **Agree with most points. Refresher training as necessary.** . NOTE: Broad statement "Notwithstanding that in our judgment, the facts show Actavis Totowa exercises adequate control through its quality unit, we recognize that the company confronts considerable opportunity for improvement." NOTE ON BIG PICTURE: Responses are to specific questions and solutions are band aids. No Systems Based Solutions are being proposed or implemented.
A22		Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations	September 2006	www.fda.gov	Guidance is intended to help manufacturers implementing modern quality systems and risk management approached to meet the requirements of 21 CFR parts 210 and 211. The guidance is not intended to place new expectations, or replace CGMP requirements to assist in their compliance.
A23		Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa LLC Inspection Conducted 18 September to 11 October 2006 Taft Road, Totowa, NJ	17 November 2006 (Cover Date)	ACTAV00002934	This report was issued following an inspection conducted by FDA starting from 18 September to 11 October 2007. This inspection was of the packaging, labeling and testing facility conducted under Special Audit Assignment. A General GMP inspection was also conducted. There were 3 Observations cited in the Form 483 which was issued for the inspection. These included:

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					• 1- Deviations from written specifications, test procedures and laboratory mechanisms are not justified • 2- The accuracy, sensitivity and reproducibility of test methods have not been established • 3- Verification of the suitability of the testing methods is deficient in that they are not performed under actual conditions of use.
A24		e-mail from John Deiriggi to Hal Korman Fw: Actavis-Digitek	4 January 2007	Plaintiff's Exhibit M21	"I believe that we should seriously consider looking at either manufacturing the product here as an alternate site to Amide." NOTE: This is in response to Walter H. Owens Senior Vice President R&D Chemistry Mylan Pharmaceuticals, Inc. who states in the e-mail chain "Overall I am concerned with the long-term viability of Amide, either through quality issues or contract issues. The next course of action being taken is that Joe Duda's group and Legal will be contacting Actavis to try and get clarity as to what they want to do with the contract."
A25		Warning Letter 07-NWJ-06 to Divya Patel, President Actavis Totowa, LLC Little	1 February 2007	Plaintiff's Exhibit 25	This Warning Letter was issued following a 10 July to 10 August 2006 Inspection of the Little Falls New Jersey site. The following compliance issues were raised by

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Falls New Jersey			FDA: • Significant deficiencies in Quality Unit • Laboratory notebooks don't include all raw test data and don't always document preparation and testing of samples and don't record OOS test results when obtained • Failure to check computer output and input • Failure to recognize when in-process specifications not met or not documented when discovered • No procedures for conducting bulk holding time studies • Failure to identify and control rejected in-process materials to prevent use in manufacturing • Unsatisfactory cleaning validation studies • Differences between Master and Batch Production records • Equipment used in manufacture not adequately qualified. • Failure to establish written procedures for maintenance of manufacturing equipment FDA was not convinced that promised efforts address the quality of the drugs already released to market and requests a third-party audit.
A26		Internal Document "The 302	22 May	ACTAV001420149	Internal project management sheet shows Digoxin lot

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Sample Batches with Questions Manufacturing Review"	2007		5453A which may have been manufactured in 2005 shows "Tablet OOS for weight on the QA Over Check Data Sheet" indicating continued problems with Digoxin tablet weight variability.
A27		Digoxin Tablets, USP 0.25 mg Annual Product Review January 1 2006 to December 31 2006	3 April 2007	Plaintiff's Exhibit 253	This annual product review had the following findings: • 44 batches manufactured for a total of 184,800,000 total tablets • 17 Adverse events were noted including some for o Atrial fibrillation o Elevated Digoxin level in blood o Orthostatic hypotension o "Unknown" potency question • Detail of investigations was limited due to inability to trace product in market to lots produced at plant • One lot, 60319A Final Blend Assay Standard Deviation was 4.5% which was higher than other batches • Some additional Content Uniformity and Dissolution values were "slightly higher" compared to other batches reviewed.
A28		UDL Laboratories, Inc. Receiving Inspection Form for receipt of 0.25 mg Digitek Tablets	28 June 2007	Plaintiff's Exhibit M65	Notes that "4 tabs out of UDL's thickness tolerance". NOTE: UDL has tighter specifications on thickness than Actavis because of blister packaging needs.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A29		Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa LLC Inspection Conducted 5 September to 28 September 2007 Little Falls, NJ	5 September to 28 September 2007	Plaintiff's Exhibit 158	This report was issued following an inspection conducted by FDA starting from 5 September to 28 September 2007. This inspection was conducted as a follow-up to Warning Letter # 07-NWJ-06. The inspection provided general GMP coverage as well as pre-approval coverage to one product. Inspection guidance afforded through CPGM 7356.002 and CPGM 7346.832. There were 3 Observations cited in the Form 483 which was issued for the inspection. These included: • An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning failure of one or more distributed batches of drug to meet the specifications established for it in the application (stability failure) • Written stability testing program is not followed (36 month pull not tested for four products • Written production and process control procedures are not followed in the execution of production and process control functions (DOP #0033 Investigations of Out of Specification Results and DOI # QC-059 are not followed)
A30		e-mail 1 October 2007 From Sarita Thapar to Saira Rizvi	1 October 2007	Plaintiff's Exhibit 249	E-mail lists "….top 3 products with AER's associated with death or permanent injury…" Last years answer

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Regarding Insurance Questions			[2006] Digoxin 0.25 mg.
A31		Incident Report for Digoxin 0.125 mg Control # 70924A1	30 November 2007	Plaintiff's Exhibit 44	Two tablets of Digoxin tablets 0.125 mg were found with approximately double the thickness from counter channels during packaging/filling operation on packaging line #405. Individuals present or included on investigation were: • Vilas Patel (line lead person) • Dilip Joshi (packaging manager) • Ashesh Dave (director of packaging) • Aida Ruiz (QA supervisor) • Dan Bitler (QA director) Although initially halted, production continued under "a watchful eye" following a visual only inspection
A32		Investigation of Deviation Report: Digoxin Tablets 0.125 mg (145), Investigation Log No. 07-093 Product Lot No. 70924A1	5 December 2007	Plaintiff's Exhibit 16	Description of Problem: Two tablets of Digoxin tablets 0.125 mg were found with approximately double the thickness from counter channels during packaging and filling operation. No root cause determined. Batch 709242A1 put on hold by QA. Deviation is considered an isolated incident; therefore no other batches are impacted. No Chemical Testing was Conducted.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A33		Memorandum from Li Radtke to Executive Staff at UDL Laboratories, Inc. Regarding Actavis Totowa Re-Assessment Summary	21 January 2008	Plaintiff's Exhibit M45	Delineates recalls of products: • August 10, 1995 Incorrect package insert • December 1990 Variation in tablet size resulting in sub- and super-potency.
A34		Digoxin Blend Failure Investigation	Unknown. (Probably last quarter 2007)	Plaintiff's Exhibit 159	Notes increase in blend analysis failures from sampling changes. Lots include 70148A and 70207A. Potential causes: • Blend sampling procedures (change over to slugs) • Low humidity/high sampling • API particle size • Batch record problems • Method issues • Product validation • Laboratory testing Relative humidity levels were noticed to be lower for months of October through April. Dryer conditions may lead to electrostatic attractions which may be the cause for the higher number of blend failures. Blend was subject to additional testing, which it passed, and released.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A35		URGENT: DRUG RECALL Digitek (Digoxin tablets, USP) from Actavis to Valued Customer	24 April 2008	Plaintiff's Exhibit 113	States "This recall notice has been initiated due to overweight tablets. Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be observed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arryhythmia) due to lack of therapeutic efficacy."
A36		UDL Internal Investigation Record from Digitek Tablets, .125 mg and .250 mg	15 May 2008	Plaintiff's Exhibit M69	Investigation summary states "….One complaint for Digitek 125 mcg (#08-038) reported that the customer observed that the tablets appear smaller than usual and that her heart starting racing. This complaint was forwarded to PSRM on 3/18/08 for investigation and it remains open." NOTE: This complaint was before any recall notice.
A37		Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa	After 20 May 2008	Plaintiff's Exhibit 91	This report was issued following an inspection conducted by FDA starting from 18 March 2008 to 20 May 2008. This inspection was conducted as a

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		LLC Inspection Conducted 18 March to 20 May 2008 Riverview New Jersey			qualifying GMP inspection for the new Riverview facility. The inspection provided general GMP coverage. Pre-approval coverage was not planned or conducted. Inspection guidance afforded through CPGM 7356.002 and CPGM 7346.832. There were 11 Observations (with significant detail and example) were cited in the Form 483 which included: • 1-The responsibilities and procedures applicable to the quality control unit are not fully followed • 2-Drug products failing to meet established specifications and quality control criteria are not rejected. • 3-There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed • 4-Determinations of conformance to appropriate written specifications for acceptance are deficient for in-process materials • 5-Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identify, strength, quality and purity. • 6-Investigations of an unexplained discrepancy and a

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy • 7-An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application. • 8-Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications • 9-Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance. • 10-Changes to written procedures are not reviewed and approved by the quality control unit. • 11-Drug product production and control records are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed
A38		Actavis Totowa, LLC	11 June	ACTAV001302483	These Form 483 observations were specifically

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		Response to FDA by Sigurdur Olafsson, Deputy CEO, Actavis Group, CEO Actavis, Inc. by Form 483 Observations as a Result Inspection of Actavis Totowa Inspection Conducted 18 March to 20 May 2008 Riverview New Jersey	2008		addressed by Sigurdur Olafsson, Deputy CEO, Actavis Group, CEO Actavis, Inc. In the cover letter he makes the statement "It is quite fair to say, as we related ion our April 28, 2008 letter that Actavis Totowa prides itself in maintenance of CGMP compliance by virtue of comprehensive and robust quality systems. Thus we were surprised and chagrined as the last inspection developed by our failure to have secured the compliance we had sought and committed to establish at Actavis Totowa. In recognition of that situation, which we concede is largely reflected in the Form 483 observations listed below, we took the following actions: • All product manufacturing and distribution was suspended. • A highly qualified team of consultants from PAREXEL was engaged to assist Actavis Totowa in a complete evaluation of all its quality systems and the Company's products. • With the respect to previously distributed product, PAREXEL is conducting a thorough risk assessment pursuant to a protocol that has been provided to the agency on May 30 2008. • The Company has reduced the number of products in its portfolio and, thus the number of batches that need to be supported by its quality system. • Resumption of manufacturing will entail notice to

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					FDA and be gradual and measured. The Company PAREXEL will conduct comprehensive assessments to determine whether manufacturing can be supported by pertinent qualifications and validations, and whether Procedures adequate for in-process finished product and post-marketing monitoring and controls are in place. Only then will a product be suitable for release and distribution. As may be appropriate, equipment may be re-qualified, and methods and processes revalidated. • Until such time as the Company determines that the Company's product release systems are sufficiently robust and reliable, PAREXEL will audit Company release decisions and must concur before product is distributed. • Product currently in warehouses continues to be quarantined. Although the Company had concluded that certain batches were suitable for distribution based on its assessments and risk-based assessments by PAREXEL, and resumed limited distribution for a short period of time, it has suspended that distribution. There are no plans to resume distribution of previously manufactured product. • As part of our restructuring and corrective action initiative, we shall adopt procedures that require that Actavis, Inc. management be regularly informed concerning site Quality Systems and CGMP

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					compliance. • Actavis Totowa has filed reports with the agency on a regular basis to provide updated information. We shall continue to do so, with the minor modification that such updates will henceforth be monthly, rather than weekly to more efficiently capture material developments. Responses to specific Form 483 observations are generally accepted at face value however; where they are incorrect (e.g. Observations 5 with respect to equipment qualification) are not agreed to.
A39		Investigation # 08-060: Digoxin Tablets 0.125 mg (125) Lot # 80228A1 1 April 2008	1 April 2008	Plaintiff's Exhibit 141	Overweight tablets were found during packaging. Preliminary investigation showed a 5000 count bottle had 17 out of 30 tablets above 120 mg. Put on hold pending QA investigation.
A40		Health Hazard Evaluation – Digoxin Tabs 01.25 mg	18 April 2008	Plaintiff's Exhibit 220	Concludes double thick tablets could lead to digitalis toxicity. Can result in death. Thin tablets may cause congestive heart failure and arrhythmia.
A41		e-mail from Wanda Eng to Phyllis Lambridis Regarding Potential 483 items.	17 April 2008	Plaintiff's Exhibit 146	Detailed list of potential 483 items. NOTE: Ms. Eng during deposition claims that these were not specific observations related to the company but based on her past experience.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A42		Establishment Inspection Report (EIR) for FDA Inspection of Actavis Elizabeth LLC Inspection Conducted 21 April to 21 May 2008 Elizabeth New Jersey	6 June 2008 (from 21 April to 21 May)	Plaintiff's Exhibit 80	This inspection was conducted as a follow-up to Warning Letter 06-NWJ-15 which was issued on 15 August 2006. Inspection guidance afforded through CPGM 7356.002 and CPGM 7346.832. Major areas of review included 15-day reports, late reporting, periodic reports, deactivated cases, medical inquires, lack of effective complaints and written procedures. There were 4 Observations cited in the Form 483 which included: • 1- Adverse drug experience information had not been reported to FDA (continuing problem from 2006) • 2-ADE's not reported to FDA in 15-day required time frame which were either serious or unexpected • 3-Failure to send periodic (quarterly) reports to FDA (substantially redacted) within 30 days of the close of the quarter • 4-The flow of in-process materials through the building is not designed to prevent contamination
A43		Actavis Totowa, LLC Response to FDA Form 483 Observations as a Result Inspection of Actavis Totowa Inspection Conducted 21	6 June 2008	ACTAV000028820	Responses to the Form 483 observation are summarized below: • 1- Adverse drug experience information had not been reported to FDA (continuing problem from

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		April to 21 May 2008 Elizabeth New Jersey			2006) **Agreed to observation Purchase of Alpharma will enhance all reporting** • 2-ADE's not reported in 15-day required time frame to FDA either serious or unexpected. **Agreed, working on system. Root cause was non-US events.** • 3-Failure to send periodic (quarterly) reports to FDA (substantially redacted) within 30 days of the close of the quarter. **Agreed, working on system. Root cause was non-US events.** • 4-The flow of in-process materials through the building is not designed to prevent contamination. **Agreed with finding, implementing corrective actions.**
A44		e-mail from Howard W. Martin to Tammy Maisel, RE: Actavis Totowa Recall, Good Think UDL pulled these products	21 July 2001	Plaintiff's Exhibit M64	e-mail states "Good thinking, UDL pulled these products and put them aside when Digitek broke". Indicating that Mylan and UDL recognized in advance that the problems related to Digitek were not limited to Digitek and took pre-emptive initiatives.
A45		Complaint for Permanent Injunction United States of America v. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur	14 November 2008	Plaintiff's Exhibit 82	Detailed account of five FDA inspections over last three years (2005 to 2008) Five inspections over three years revealed numerous and reoccurring violations of CGMP requirements examples include:

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		Oli Olafsson, Douglas Boothe			• Failed to investigate OOS testing results • QA didn't initiate OOS investigations • Failure to verify suitability of methods • Failure to record and justify deviations from written procedures • Deviated from written procedures and specifications • Test methods didn't work as intended • Failure to follow written stability program • Failure to investigate failed batches
A46		e-mail from Richard Dowling to Bharat Patel Regarding New Punches for Digoxin	18 December 2007	Plaintiff's Exhibit 97	Document states "As part of the corrective action for investigation number 07-093 for Digoxin double tablets, I am going to state that we will buy a complete set of lowers and dies for both strengths of Digoxin that will be dedicated and not used for any other products. It is possible the tablet stuck to the punch and was double compressed".
A47		Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, Douglas Boothe	23 December 2008	Plaintiff's Exhibit 214	Detailed agreement "….establish and document management controls over Quality Assurance (QA) and Quality Control (QC) for the Actavis Totowa Facilities."
A48		Digoxin Tablets, USP 0.125	Draft	Plaintiff's Exhibit	This annual product review had the following findings:

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		mg Annual Product Review January 1 2008 to December 31 2008		144	• Manufactured 19 batches and 8 were rejected • Rejection came only after FDA inspection which prompted company to do voluntary recall of the product due to the potential for double thick product on market • 22 ADE/Product complaints were reported
A49		Memorandum from UDL Li Radtke to Executive Staff Regarding Actavis-Totowa Re-Assessment	21 January 2008	Plaintiff's Exhibit M45	Summary of Regulatory Affairs/Compliance's evaluation of Actavis Totowa. Lists following [redacted] recall history: • August 10, 1995 Class II recall for incorrect package insert • December 1990 Class II recall for variation in tablet size and resulting in sub and super potency
A50		e-mail From Sigurdur Oli Olafsson to Mark Keatley Regarding Inquiry About Financial Impact of Digitek Problems	2 May 2008	Plaintiff's Exhibit	e-mail was responded to with "I suggest we talk about this – don't put this on e-mail." Financial impact questions include: • What is FY 2008 revenue and gross margin for product? • Any deaths or injuries alleged against us? • Are we covered by insurance vs. product/process

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					liability and Mylan liability? • Estimated recall cost only for this product • Need Digitek answers asap
A51		e-mail from Jeffrey Rope to Grudrun S. Eyjolfsdottir CC: Chris Young Regarding FDA Update	3 May 2008	Plaintiff's Exhibit 227	This e-mail communicates potential upgrades, corrective actions and observations with respect to ongoing FDA actions. Of note are the following: • Have recommended purchase of 3-4 new PTK [tablet] presses with compaction force weight control and automatic reject. • Digoxin presses will be fitted with Kramer de-duster to protect operators from Digoxin tablet dust during packaging. • "In my view it is totally unacceptable that our people cannot read English operating procedures and batch records."
A52		e-mail from Suzanna Wolfe to Connie Hatcher, Mylan Pharmaceuticals, Inc. QA Manager, Outsourced Products & QA Compliant Investigations RE: Digitek parameter review	4 January 2008	Plaintiff's Exhibit M14	e-mail states "Connie- 70926A1 and 70953A1 have low assay (96.2 and 97.3%). We are looking for 71004A1."

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
A53		Mylan Internal Memo to File 23 January 2008 Final Corrective Action Memo-Audit XA-06-010. Date of Inspection was 8-9 November 2006	23 January 2008 (8-9 November 2006)	Plaintiff's Exhibit 136	Summary of Mylan CGMP Audit of Actavis Totowa LL, at Little Falls, NJ for Digoxin Tablets 0.125 mg and 0.25 mg. Of note are the following: • Audit was originally conducted 8-9 November with report completed 4 December 2006 • States that "There is no Quality Agreement in place with Actavis Totowa LLC • Mylan admits to not conducting an in-depth systems audit but took Vice President of Regulatory and Qualities word for status of compliance with CGMPs and appropriateness of response to FDA • Several statements of "Documents to be provided later". • Digoxin manufactured exclusively for Mylan • Dated equipment noted • Quality Control laboratory area was congested • Warehouse for containers and closures was leaking water form the ventilation system and smelled of mildew upon entering. • Copies of important documents still not provided o Actavis response to August 2006 Warning Letter o Summary of Digoxin complaints submitted to FDA o Correspondence with FDA regarding complaints o Periodic updates with FDA regarding QSIP o FDA 483 observations and responses to the

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					September 2006 inspection
A54		e-mail From Misbah Sherwani to unknown individual 15 April 2008 FW: List by Product Attach: 5-Sep-07 Present Investigations by product.xls	15 April 2008	Plaintiff's Exhibit 217	Spreadsheet contains an entry which states: "Operator noticed tablets that were thinner than a typical tablet during inspection of drum #2". Investigation number 08-030 for Lot Number 80133A.
A55		Recall-Firm Press Release on FDA Website: Actavis Totowa (formerly known as Amide Pharmaceutical, Inc.) recalls all lots of Bertek and UDL Laboratories Digitek (Digoxin tablets, USP) as precaution	25 April 2008	www.fda.gov	Class I recall notice. "The voluntary all lot recall is due to the possibility that tablets with double the appropriate thickness may have been commercially released. These tablets may contain twice the approved level of active ingredient than is appropriate".
A56		e-mail from Chuck Koon to Hal Korman regarding Actavis (Amide) Recall and FDA Inspection	27 April 2008	Plaintiff's Exhibit M25	Appropriate excerpts "Well over a year ago, we (Quality) presented a review of the compliance issues at Amide to the outsourced committee that was meeting regularly at this time." "Though Amide was always required to notify us of any FDA actions, not only did they not ever do that but, when we contacted them we got nowhere".

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
					"The outsourced committee was reviewing the language in the 10-year contact to see if there was any "out" for us."
A57		URGENT DRUG RECALL letter for Digoxin by Actavis	28 April 2008	Plaintiff's Exhibit 120	"This recall has been initiated due to overweight tablets." Also states "Death can result for excessive digitalis intake" and …exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia due to lack of therapeutic efficacy". Customers in this case are pharmacists not patients.
A58		e-mail From Mylan Jennifer Urso to Jill Abraham 30 April 2008 FW Dig recall	FW: 30 April 2008	MYLN000932683	"…CSC reports finding a card of Digoxin with one double thickness tablet at GL-Gloucester. The card had 4 tablets remaining- one of which was she reported as obviously double thickness." "Lynne brought this to my attention as it was reported to some facilities yesterday by pharmacy consultants that their supplies were not affected by this recall….Fortunately, the facility knew otherwise."
A59		e-mail From Mike Adams, Executive Director QA Compliance, Mylan Pharmaceuticals, to a large number of staff members updating status of Digitek	6 May 2008	Plaintiff's Exhibit M30	References a conference call with Quality, PSRM and Actavis to get information update from Actavis. Salient points include: • "Actavis is setting up a process for consumers to obtain a blood test (through Quest)"

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		recall			• "Actavis has addressed over 2,500 medical questions since April 25 2008" • Total call volume to Stericycle since recall notice 128,768
A60		General Systems Applicable to Oxycodone IR (Attachment A)		ACTAV00126195	This document very clears defines previous Quality System failures by specific Quality System and delineates how deficiencies are being addressed. NOTE: This is the "After" picture in the quintessential "Before and After" picture scheme.
A61		Response to FDA 483 Issued to Actavis Totowa 20 May 2008	11 June 2008	Document provided by Miller Law Firm	"Thus, we were surprised and chagrined, as the inspection developed by our failure to secure the compliance we had sought and committed to establish at Actavis Totowa" NOTE: Admission of failure.
A62		e-mail from Howard W. Martin to Tammy Maisel regarding Actavis Totowa recall-	21 July 2008	Plaintiff's Exhibit M64	Shows UDL anticipated site wide recalls at Actavis and purposely held product prior to expanded recall announcements.
A63		Recall-Firm Press Release on FDA Website: Actavis Totowa Announces Voluntary Recall at the Retail Level of	1 August 2008	www.fda.gov	Announces 66 product recalls.

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		All Drug Products Manufactured at its Little Falls, New Jersey Facility			
A64		e-mail from Paul Galea to Tony	2 February 2009	Plaintiff's Exhibit 73	QRB (Quality Review Board) Minutes from 26 January 2009. One page titled "Little Falls Product Complaints by Category (August 2008 to January 2009): 9 reports of Double Thickness (Digoxin Tablets).
A65		e-mail form Phyllis Lambridis to Dan Bitler RE: Mylan/Bertek Quality Head	30 April 2008	Plaintiff's Exhibit 140	e-mail states "It is my understanding that Robert and Siggi have committed to stop producing Digoxin until we have tableting equipment with weight controls. Please do not have any conversations with customers unless you have the full story.
A66		e-mail form Wanda Eng to Apurva Patel Subject: Blend Failure locations	20 July 2007	Plaintiff's Exhibit 140	Points out 19 lots with blend failures (all have OOS numbers). Two lots are for Digoxin Tablets (70148A and 70207A) manufactured on 17 February 2007 and 12 March 2007 respectively. Lot 70148A was rejected after additional testing and lot 70207A was released.
A67		e-mail form Ashok Nigalaye to Bharat Patel Subject: FW: equipment Quote	21 July 2001	Plaintiff's Exhibit 259	An equipment quote #26943 from DLS Enterprises for tablet presses with weight and thickness controls. Other equipment types enclosed in the paper work.
A68		e-mail form Ashok Nigalaye	12 July 2008	Plaintiff's Exhibit	An equipment quote #26943 from DLS Enterprises for

#		Document Title or Description	Creation Date	Exhibit #	Description of Content
		to Divay Patel, CC: Jasmine Shah, Apurva Patel, Bharat Patel Subject: FW: equipment Quote		258	tablet presses with weight and thickness controls. Lead-in e-mail states machines are similar to Stokes BB2s.
A69		Mechanisms, Manifestations and Management of Digoxin Toxicity in the Modern Era	2006	Adis Data Information, BV. Purchased online	Am. J. Cardiovascular Drugs 2006:6(2), 77-86

Attachment B:

Summary of Some FDA Actions Against Amide/Actavis

#		DATE		FDA ACTIONS		NOTES
B1		28 July to 9 August 1983		FDA Inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Four FDA Form 483 observations following establishment inspection. These include: 1. No stability data to support expiration 2. Problems with label control 3. Reconciliation of finished batch granulation with tablet cores 4. Batch records changed without proper study or approval		This was the very first inspection of Little Falls by FDA following business start up 1 May 1983. Corporate Officers presented to FDA were: • Kenneth Kolomer, President • Barry Ballan, Vice President Marketing • Ajit Desai, Vice President Quality Assurance • J.K. Shah, Vice President Production • Bharat Patel, Vice President Compression/Encapsulation NOTE: FDA writes J.K. Shah to have had 12 years experience in tablet/capsule manufacturing when he states in his 26 March 2010 deposition that he had significantly less at this point in operation. NOTE: J.K. Shah states Chandu Patel

#		DATE		FDA ACTIONS		NOTES
						was founder of the company but FDA states Kenneth Kolomer as President in 1983. Bharat Patel has 3 years experience in tabletting and encapsulation. Reference: Document retrieved via FOI Services www.foiservices.com
B2		1984-1989		FDA Inspection(s) of Amide Pharmaceutical, Inc. Little Falls New Jersey between September 1984 to March 1989 where significant violations were discovered and documented. Specific problems which led to a Consent Decree were discovered by FDA in 1987 and 1989 inspections.		Reference: Within EIR issued Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Conducted 5 to 20 December 1989 and 2 to 15 February 1990 Reference: Jasmine Shah deposition 26 March 2010 p. 120 Reference: Document retrieved via FOI Services www.foiservices.com
B3		20 April 1989		Voluntary agreement between FDA and Amide Pharmaceuticals to correct GMP deficiencies discovered during previous inspections		Reference cited in summary of findings for EIR dated 12/5-8,11, 13-15, 19, 20/89 Reference: Document retrieved via FOI Services www.foiservices.com

#		DATE		FDA ACTIONS		NOTES
B4		5 to 20 December 1989 to 15 January 1990		FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey to assess the firms compliance with voluntary agreement dated 20 April 1989. Form 483 issued (6 pages)		Reference: EIR issued Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Reference: Document retrieved via FOI Services
B5		December 1990		Class II product recall for variation in tablet size resulting in sub and super potent drug product		Reference: Plaintiff's Exhibit M45 First Product Recall
B6		Consent Decree of Injunction 92-513, 23 March 1992		"Amide perpetually restrained and enjoined from introducing and delivering for introduction into interstate commerce any article of drug that the defendants have manufactured, processed, packed, tested, or labeled and manufacturing, processing, packing, testing, labeling, holding or doing any other act with respect to any article of drug while such drug is held for sale after one or more of its components have been shipped in interstate commerce, unless and until;"		Specific points under Consent Decree include: • QA personnel inadequate in number and have background, education, training, experience or combination therein • QC laboratory personnel inadequate in number and don't have background, education, training, experience or combination therein • Not all laboratory and analytical procedures validated • Laboratory practices don't reflect actual written SOPs and be followed

#		DATE		FDA ACTIONS		NOTES
						• Records required by GMPs not kept and recorded at the time events occurred • Validations need to be reviewed by third party • Laboratory instrument procedures need to be reviewed by third party • Laboratory analyst need be trained by third party for each type of instrumentation • Manufacturing methods, facilities and controls to be need to be reviewed by a third party • All products need to be certified by third party Reference: Document retrieved via FOI Services www.foiservices.com
B7		12 December 1992 to 27 January 1993		First FDA inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey conducted following Consent Decree. Form 483 issued.		Reference: Plaintiff's Exhibit 235
B8		9 to 17 March 1993		FDA follow-up inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey conducted to review previous inspection commitments. Form 483 issued.		Reference: Plaintiff's Exhibit 235
B9		9 March to 17		FDA inspection conducted. Form 483 issued		Reference: Plaintiff's Exhibit 235

#		DATE		FDA ACTIONS		NOTES
		March 1994				
B10		14 February to 16 March 1995		FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued. FDA specifically cites errors in dissolution testing procedures for Digoxin tablets.		This was an inspection for Digoxin Batch Certification. Digoxin production started after this inspection Reference: Plaintiff's Exhibit 235
B11		8 June 1995		FDA issues batch certification to Amide for authorization to sell Digoxin under the Batch Certification Regulation 21 CFR 310.500.		Reference: Plaintiff's Exhibit 235
B12		10 August 1995		Class III product recall for incorrect package insert		Reference: Plaintiff's Exhibit M45 Second Product Recall
B13		23 April 1996		FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued.		Reference: Plaintiff's Exhibit 235
B14		12 July 1996		Amide requests FDA lift Consent Decree, FDA does not grant request		First request to lift Decree Reference: Plaintiff's Exhibit 235
B15		25 October 1996		FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey at request of Amide in an attempt to lift Consent Decree. FDA denies request and issues Form 483.		Second request to lift Decree Reference: Plaintiff's Exhibit 235

#		DATE		FDA ACTIONS		NOTES
B16		4 November 1996 to 1 December 1997		FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey in an attempt to lift Consent Decree. FDA denies request and issues Form 483.		Third request to lift Decree Extensive GMP issues still existed during this inspection. Form 483 observations were in 21 parts. “The current inspection revealed several GMP deficiencies which include incomplete impurity profile testing on finished product, failure to identify all known starting impurities, and inadequate cleaning validation for all ANDA's. In addition, the firm lacked the following: a written SOP detailing water sampling procedures; validation data to justify hardness specifications; an audit trail for HPLC data collection and entry; an adequate calibration and maintenance program to assure that critical parameters are within acceptable limits for the HPLC system; stability data to support the expiry on in-house standards; formal written investigations for all validation deviations; and environmental monitoring devices in storage warehouses. The firm's QC laboratory notebook data revealed that on several occasions, the analysts reinjected a solution or reanalyzed a

#		DATE		FDA ACTIONS		NOTES
						chromatogram with no justification or explanation; also the firm's use of SOP #030, Alternate Manufacturing Procedure, is inadequate in that the firm could not clearly define the difference between PDR (Planned Deviation Report) and an EDR (Emergency Deviation Report). The use of SOP #033, Product Related Investigations, is inadequate in that the initial date for investigations is not documented or recorded. And that there is no timeframe for when an investigation should be completed. The use of DOl QA #022, Rejecting an Item, is inadequate in that the procedures are not representative of the actual steps for product destruction. Additionally, the firm cannot track the In-Process and Finished Product Rejection Reports to the actual destruction manifests." Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services www.foiservices.com
B17		2 April 1998		FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey for sample inspection. Form		Reference: Plaintiff's Exhibit 235

#		DATE		FDA ACTIONS		NOTES
				483 issued.		
B18		2 December 1998 to 8 January 1999		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued. Amide request lifting of Consent Decree but FDA denies request.		Fourth request to lift Decree Reference: Plaintiff's Exhibit 235
B19		29 November to 8 December 1999		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued		Reference: Plaintiff's Exhibit 235 Reference: Plaintiff's Exhibit 233
B20		23 December 1999		Amide receives Digoxin Tablets ANDA approval		Reference: Plaintiff's Exhibit 235
B21		8 to 23 May 2000		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued		Reference: Plaintiff's Exhibit 235
B22		29 October to 29 November 2001		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued		Reference: Plaintiff's Exhibit 235
B23		10 June 2002		Amide released from terms of Consent Decree 10 years after document was signed.		Reference: Plaintiff's Exhibit 235
B24		11 October		FDA issues Warning Letter to Mr. Chandu Patel, Amide		Reference: Plaintiff's Exhibit 233

#		DATE		FDA ACTIONS		NOTES
		2002		Pharmaceutical, Inc. Little Falls, New Jersey		Reference: www.fda.gov First Warning Letter
B25		24 March to 25 April 2003		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued		Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services www.foiservices.com
B26		14 to 25 April 2003		FDA conducted inspection at Taft Road, Totowa, New Jersey. Form 483 issued		Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services Reference: Plaintiff's Exhibit 233
B27		12 to 21 August 2003		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued		Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services Reference: Plaintiff's Exhibit 233
B28		15 November to 1 December 2004		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued		Reference: Document retrieved via FOI Services Reference: Plaintiff's Exhibit 233

#		DATE		FDA ACTIONS		NOTES
B29		31 May to 7 June 2005		FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Warning Letter issued		Reference: Document retrieved via FOI Services Second Warning Letter
B30		10 January to 8 February 2006		FDA conducted inspection of Amide Pharmaceuticals, Inc. Little Falls New Jersey. Form 483 issued		Reference: Document retrieved via FOI Services Plaintiff's Exhibit 79
B31		1 February to 6 March 2006		FDA conducted inspection of Actavis Pharmaceuticals, LLC/Purepac Elizabeth New Jersey. Form 483 issued		Reference: Document retrieved via FOI Services
B32		10 July to 10 August 2006		FDA conducted inspection of Actavis Totowa, LLC Little Falls New Jersey. Form 483 issued		Reference: Document retrieved via FOI Services Plaintiff's Exhibit 68, 90, 52
B33		15 August 2006		FDA Issues Warning Letter in response to January-February 2006 inspection		Reference: Plaintiff's Exhibit 229, 233, 246 Reference: www.fda.gov Third Warning Letter
B34		18 September to 11 October		FDA conducted inspection of Actavis Totowa, LLC, Totowa New Jersey, Taft Road. Form 483 issued		Reference: Document retrieved via FOI Services www.foiservices.com

#		DATE		FDA ACTIONS		NOTES
		2006				Plaintiff's Exhibit 228
B35		13 December 2006 to 29 January 2007		FDA conducted inspection of Actavis Elizabeth, LLC, Elizabeth, New Jersey. Form 483 issued		Reference: Document retrieved via FOI Services www.foiservices.com
B36		9 January 2007		FDA Issues Warning Letter to Divya Patel, Actavis Totowa, LLC		Reference: www.fda.gov Plaintiff's Exhibit 231 Fourth Warning Letter
B37		1 February 2007		FDA Issues Warning Letter to Divya Patel, Actavis Totowa, LLC		Reference: www.fda.gov Plaintiff's Exhibit 2 Fifth Warning Letter
B38		5 to 28 September 2007		FDA conducted inspection of Actavis Totowa, LLC, Little Falls, New Jersey, Form 483 issued		Reference: Document retrieved via FOI Services Plaintiff's Exhibit 50, 157, 158, 171
B39		18 March to 20 May 2008		FDA conducted inspection of Actavis Totowa, Riverview Dr, Totowa, New Jersey, Form 483 issued		Reference: Document retrieved via FOI Services Plaintiff's Exhibit 91

#		DATE		FDA ACTIONS		NOTES
B40		21 April to 21 May 2008		FDA conducted inspection of Actavis Elizabeth, Elizabeth New Jersey, Form 483 issued		Reference: Document retrieved via FOI Services
B41		25 April 2008		Voluntary recall of all Digoxin tablets agreed to with FDA.		Reference: www.fda.gov Third Recall
B42		24 to 27 June 2008		FDA conducted inspection of Actavis Mid-Atlantic, Owings Mills, Maryland, Form 483 issued		Reference: Document retrieved via FOI Services
B43		1 August 2008		Voluntary recall of all products manufactured at Little Falls, NJ site agreed to with FDA.		Total of 66 products recalled. Reference: www.fda.gov Fourth Recall
B44		14 November 2008		Complaint for Permanent Injunction United States of America v. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, Douglas Boothe		Reference: Plaintiff's Exhibit 82
B45		23 December 2008		Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, Douglas Boothe		Reference: Plaintiff's Exhibit 214

#		DATE		FDA ACTIONS		NOTES
B46		20 February to 31 March 2009		FDA conducted inspection of Actavis Totowa, Little Falls, New Jersey, Form 483 issued		Reference: Document retrieved via FOI Services www.foiservices.com
B47		18 February 2010		FDA Issues Warning Letter to Douglas Boothe, Actavis US, Morristown, New Jersey		Reference: www.fda.gov Sixth Warning Letter

1983 to 2010 (27 Years)

Event		Number		Notes	
Number of Form 483s=		26		First Form 483 issued in 1983; Last Form 483 Last in 2009. Most have numerous observations	
Number of Warning Letters =		6			
Number of Consent Decrees =		2			
Number of Refusals by FDA to Lift First Consent Decree =		3			
Number of Product Recalls =		4		1990 Class II: Super or sub potent tablets due to thickness 1995 Class III: Incorrect package insert	

Event		Number		Notes	
				2008 25 April, Class I Digoxin double thick or super potent 2008 1 August, total product recall from Actavis Totowa Little Falls , New Jersey Site, 66 products total	

Appendix C:

Some Historical Facts Regarding Digitek Tablet Manufacturing: Approximate Chronological Order

1. Digoxin has been used as a heart drug for over 230 years. Digoxin tablets have been on the market in the United States since 1938. (Reference: See Attachment A69)

2. Digoxin has a narrow therapeutic index which means that a very narrow range of concentration in the bloodstream must be maintained or toxicity or lack of effect can occur. (Reference: See Attachment A69)

3. Difficulty in manufacture of Digoxin tablets has been known for some time and a concern to FDA early on. This fact prompted Congress to pass the Digoxin Regulation in 1974 (21 CFR Part 310.500) which required manufacturers of Digoxin tablets to submit their products to FDA for certification. (Reference: See Attachment A10)

4. June 1995 FDA issues certification to Amide Pharmaceuticals allowing them to manufacturer and sell Digoxin under the Batch Certification Regulation 21 CFR 310.500. (Reference: See Attachment B11)

5. Continued product safety concerns by FDA prompted the repeal of 21 CFR 300.15, thus requiring the submission of an NDA by the product innovator Burroughs-Welcome, which was approved in 1995 with the trade name Lanoxin. (Reference: See Attachment A10)

6. During the same period, Amide executed an extensive year long product development effort to formulate, manufacture and collect data to support submission of an ANDA for Digoxin tablets, thus confirming the concern FDA has with respect to the difficulties associated with manufacturing Digoxin tablets. Amides efforts resulted in at least 40 to 50 experiments before the proper formulation was achieved. (Reference: See Attachment A7)

7. Process validation which was included in the ANDA application for Digoxin tablets occurred in mid-November 1997. Process validation did not include all strengths of the product. Process validation was performed only on 0.250 mg strength tablets. The .250 mg tablet is white and does not contain colorant. The 0.125 mg tablet is green and the 0.500 mg tablet is yellow. (Reference: See Attachment A8)

8. Successful formulation of Digoxin tables required micronization during product manufacture. Micronization is the process of transforming active ingredient and/or excipients into a fine powder. Fine powders led to problems with static

electricity during manufacturing especially during the winter months. (Reference: Attachment A7, A34)

9. On 21 February 2001 the Law Firm of McKenna & Cuneo, LLP of Washington DC argued on behalf of Bertek Pharmaceuticals and Amide for revocation of the 1974 Digoxin Regulation (21 CFR Part 310.500) to "…ensure that the marketplace does not include Digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence, formulation and manufacturing changes that have not been approved by FDA and unproven labeling claims". (Reference: Attachment A10)

10. Amide first experienced difficulties with FDA from 28 July to 9 August 1983 during its first inspection shortly after the Little Falls, New Jersey facility opened. Major findings included:

    a. Stability testing program didn't support 2 year expiration
    b. Control of labels was inadequate
    c. Personnel making unauthorized changes to batch records
    d. Unaccounted loss of material during manufacture of tablets

    (Reference: Attachment B1)

11. From September 1984 to March 1989 (~5 ½ years) FDA inspections of Amide at Little Falls finds repeated, significant violations of the CGMPs. Major findings include:

    a. Insufficient methods validation
    b. Unsound methodology
    c. Inadequate review of data
    d. Improper calibration practices
    e. Poor record keeping
    f. Lack of submission of periodic reports on ANDA products,
    g. Insufficient stability data

    (Reference: Attachment B1, B2)

12. December 1990 Class II recall initiated for variation in tablet size resulting in sub and super potent drug product, demonstrating lack of manufacturing controls since at least this time. (Reference: Attachment B5)

13. First Consent Decree of Injunction signed by between Chandu Patel, President, Amide Pharmaceutical, Inc. and US Justice Department. Specific points FDA required by include:

a. QA personnel must be adequate in number and have background, education, training, experience or combination therein
b. QC (laboratory personnel must be adequate in number and have background, education, training, experience or combination therein
c. All laboratory and analytical procedures shall be validated
d. Laboratory practices shall reflect actual written SOPs and be followed
e. Records required by GMPs shall be kept and recorded at the time events occurred
f. Validations to be reviewed by third party
g. Laboratory instrument procedures to be reviewed by third party
h. Laboratory analyst shall be trained by third party for each type of instrumentation
i. Manufacturing methods, facilities and controls to be reviewed by a third party
j. All products to be certified by third party
k. Third party to certify to FDA all actions have been taken

(Reference: Attachment B6)

14. From 23 March 1992 until 10 June 2002 Amide is frequently inspected by FDA under terms of the Consent Decree and for ANDA Pre-Approval Inspections. FDA writes numerous Form 483s with multiple observations. FDA denies Amide request to lift the Consent Decree on at least three separate occasions. (Reference: Attachment B6-B10, B13-B19, B21-B23)

15. 10 August 1995 Class III product recall initiated by Amide for incorrect package insert. (Reference: Attachment B12)

16. October 1997, Amide submits ANDA to produce Digoxin tablets using process validation data generated in 1994. (Reference: Attachment A8)

17. Amide receives approval from FDA to manufacture and sell Digoxin Tablets on 23 December 1999. (Reference: Attachment B20)

18. 9 May 2000, Adverse Drug Event for Digoxin reported to Amide: Death Occurs 2.5 hours after taking Digitek. Event not reported to FDA. (Reference: Attachment A9)

19. 29 October to 29 November 2001, FDA inspects Amide and makes the following Form 483 observations:

a. Thin tablets observed by packaging personnel
b. Visual inspection resulted in rejection of 1,600 tablets
c. FDA states no assurance that all short weight/thin tablets were rejected
d. No written rework procedure in place

e. No assurances that all 32 stations of tablet press yields tablets within specification for weight or thickness because only 10 of 32 stations were checked during operational/performance qualification studies and compression start-up.

(Reference: Attachment A11)

20. FDA Form 483 Observation for the 29 October to 29 November 2001 states:

"During the packaging of [redacted] thin tablets were observed by packaging personnel. A portion of the batch (drum 4, 7, 8, & 11) was visually inspected for the presence of thin tablets, which resulted in approximately 1,600 tablets being rejected and ultimately the rejection of drums 4, 7, 8 and 11. The entire contents of drum 1,2,3,5,6,9 and 10 were packaged. During packaging, the packaging line was run at slower speed so that thin tablets could be observed on the tracks.

- There is no assurance that all short weight/thin tablets were rejected from the batch
- There was no rework procedure written for the tablet inspection of drums
- During operational/performance qualification studies from compression start-up, 10 & 32 stations of the tablet press are checked for weight and thickness. Therefore, there is no assurance that all 32 stations of the tablet press yield tablets within specifications for weight and thickness"

As part of their response to FDA, Jasmine Shah, Director of Regulatory Affairs states:

"In order to handle this type of problem in the future, Amide has purchased tablet sorting equipment that will sort thick/thin tablets. Enclosed is a purchase order copy for the equipment (Attachment 1). Upon receipt of the equipment, an IQ/OQ/PQ will be performed and the equipment will be used if such a situation arises."

(Reference: A11, Plaintiff's Exhibit 236)

21. 10 June 2002, FDA lifts first Consent Decree (Reference: Attachment B23)

22. 8 June 2004 Amide receives complaint from a pharmacist in Bellingham, WA regarding thick Digoxin tablet. Amide confirms double thickness, no definitive root cause found. Compression occurred on tablet presses #67 or #71. Tablet manufacture occurred 6, 7 and 10 November 2003. No chemical testing conducted on product. This is the first instance of double thick Digoxin tablets reported and confirmed in market place. (Reference: Attachment A13, A14)

23. December 2003 Sigurdur Olafsson is made Managing Director of Actavis US. (Reference: p 24, Sigurdur Olafsson deposition 10 February 2010)

24. 16 July 2004 Sigurdur Olafsson begins conducting due diligence review of Amide for potential purchase by Actavis hf. He finds no problems with respect to FDA or compliance with CGMPs. (Reference: Plaintiff's Exhibit 190)

25. Formal due diligence conducted by Actavis for purchase of Amide Pharmaceutical, Inc. from July 2004 to July 2005. According to CEO Sigurdur Olafsson, outside consultants used for detailed due diligence consisting of an operation team and a quality team. No problems with respect to FDA or compliance with CGMPs. (Reference: p 50-52, Sigurdur Olafsson deposition 10 February 2010)

26. Actavis purchases Amide Pharmaceuticals on 27 July 2005. Purchase includes Little Falls Facility (main site), Taft Road Facility and Riverview Facility all within close proximity to one another. Little Falls is the original facility where most of the manufacturing and compliance related difficulties occurred. (Reference: p 24, 225 Divya C. Patel deposition 30 April 2010)

27. 15 May 2006, company named changes from Amide Pharmaceutical, Inc. to Actavis Totowa, LLC following sale to Actavis Group, hf. (Reference: Plaintiff's Exhibit 91)

28. January 2006, Sigurdur Olafsson is made President of Actavis US. (Reference: p 62, Sigurdur Olafsson deposition 10 February 2010)

29. 10 January 2006 to 8 February 2006 FDA inspects Actavis Totowa, Little Falls, New Jersey and writes a Form 483 with 8 observations. Inspection is primarily related to pharmacovilgilence. Specifics include:

    a. Adverse drug experiences not reported to FDA within proper time frame or not reported at all, including Death Associated with Digitek on 9 May 2000 2.5 hours after taking Digitek
    b. No review of literature related ADE for products
    c. No written procedures for ADEs
    d. Failure to investigate consumer complaints including a metal screw found in a bottle of product
    e. Failure to investigate OOS percent yield of bulk material
    f. No process validation
    g. Qualification and start-up procedures in manufacturing is inadequate

    (Reference: Attachment A16)

30. In e-mails from Ashok Nigalaye to Divya Patel and from Ashok to Bharat Patel dated 12 July 2006 and 21 July 2006. Discussion about purchasing new tablet presses which contain tablet weight and thickness controls, including an

equipment quote #26943 from DLS Enterprises. (Reference: Plaintiff's Exhibit 258 and 259)

31. 10 July to 10 August 2006, FDA inspects Actavis Totowa, LLC Little Falls, New Jersey. Inspectional coverage includes the Quality System, Laboratory Control System and Material System. FDA's summary statement pronounced:

    "A review of the firm's manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented."

    A Form 483 was issued with 15 observations which included:

    a. 1-The Quality Unit Lacks authority to fully investigate errors that have occurred.
    b. 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing
    c. 3- The responsibilities and procedures applicable to the quality control unit are not fully followed
    d. 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications
    e. 5- Input to and output from the computer are not checked for accuracy
    f. 6- The suitability of testing methods is not verified under actual conditions of use
    g. 7- The written stability testing program is not followed
    h. 8- Examination of testing samples is not done to assure that in-process materials conform to specifications
    i. 9- Deviations from written procedures and process control procedures are not recorded and justified
    j. 10- Master production and control records are deficient in that they do not include complete sampling and procedures
    k. 11- Equipment used in the manufacture, processing, packing, or holding of drug products is not of appropriate design to facilitate operations for intended use
    l. 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product
    m. 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable
    n. 14- Written procedures are not followed by receipt and storage of components
    o. 15- There was a failure to handle and store components at all times in a manner to prevent contamination

    Divya Patel is still the most responsible person on site, Jasmine Shah is still primarily responsible for Quality Assurance and Regulatory Affairs, and Dan

Bitler is still primarily responsible for Quality Assurance approval and sign-off. These observations are similar and consistent with what FDA has found since its first observations starting in 1983.

(Reference: Attachment A18)

32. 15 August 2006 FDA issues Warning Letter to Actavis Totowa, LLC Little Falls New Jersey regarding inspection conducted 10 January 2006 to 8 February 2006. (Reference: Attachment A19)

33. 4 January 2007 Mylan Pharmaceuticals, Inc. openly states reservations about continued relationship with Actavis.

"I believe that we should seriously consider looking at either manufacturing the product here or as an alternate site to Amide"

(Reference: Attachment A24)

34. 1 February 2007, Warning Letter issues to Divya Patel concerning 10 July to 10 August inspection findings. (Reference: Attachment A25)

35. Actavis annual product review for Digitek 0.25 mg tablets on 3 April 2007 for 1 December 2006 to 31 December 2006 finds the following:

a. 17 Adverse events were noted including some for
    i. Atrial fibrillation
    ii. Elevated Digoxin level in blood
    iii. Orthostatic hypotension
    iv. "Unknown" potency question
b. Detail of investigations was limited due to inability to trace product in market to lots produced at plant
c. One lot, 60319A Final Blend Assay Standard Deviation was 4.5% which was higher than other batches
d. Some additional Content Uniformity and Dissolution vales were "slightly higher" compared to other batches reviewed.

(Reference: Attachment A27)

36. Blend uniformity failures for different products are discussed in an e-mail from Wanda Eng to Apurva Patel dated 20 July 2007. In particular, Blend Uniformity failures for Digoxin Tablets manufactured on 17 January 2007 and 12 March 2007 are discussed. One lot was rejected after additional testing and one was released. (Reference: Plaintiff's Exhibit 183)

37. 5 September 2007 to 28 September 2007, FDA inspects Actavis Totowa Little Falls, NJ facility as a follow-up to Warning Letter. It is a general GMP inspection and a pre-approval inspection for one product. Summary of findings include:

    a. An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning failure of one or more distributed batches of drug to meet the specifications established for it in the application (stability failure)
    b. Written stability testing program is not followed (36 month pull not tested for four products
    c. Written production and process control procedures are not followed in the execution of production and process control functions (DOP #0033 Investigations of Out of Specification Results and DOI # QC-059 are not followed)

    (Reference: Attachment A29)

38. 1 October 2007 internal e-mail indicates Digoxin 0.25 mg is the top product where Adverse Drug Events are associated with death or permanent injury. (Reference: Attachment A30)

39. 30 November 2007, Double thick tablets discovered during manufacturing of Digoxin 0.125 mg tablets. Although initially halted, production continued following only visual inspection. Detailed investigation conducted within a very short period of time. Product is released to market without conclusive evidence of what caused the double thick problem on 5 December 2007. No chemical testing of tablets was conducted. (Reference: Attachment A31, A32)

40. Last quarter 2007 Digoxin Blend failure investigation conducted. Potential causes cited include:

    a. Blend sampling procedures (change over to slugs)
    b. Low humidity/high sampling
    c. API particle size
    d. Batch record problems
    e. Method issues
    f. Product validation
    g. Laboratory testing

    According to company document, relative humidity levels were lower for months of October through April. Dryer conditions may lead to electrostatic attractions which may be the cause for the higher number of blend failures. (Reference: Attachment A34)

41. In an e-mail dated 18 December 2007, Richard Dowling states to Bharat Patel:

"As part of the corrective action for investigation number 07-093 for Digoxin double tablets, I am going to state that we will buy a complete set of lowers and dies for both strengths of Digoxin that will be dedicated and not used for any other products. It is possible the tablet stuck to the punch and was double compressed".

(Reference: Plaintiff's Exhibit 97)

42. From 18 March to 20 May 2008 FDA conducted an inspection of the Actavis Totowa new Riverside facility located at 990 Riverview Drive, Totowa, New Jersey. According to the FDA:

"This inspection was limited to coverage of the Quality System due to significant cGMP deficiencies including but not limited to out of specification in-process, finished product and stability results for more than [redacted] prescription pharmaceutical products; release of Digoxin Tablets 0.125 mg, lot# 70924A2, following visual inspection of the [redacted] to remove "double thick" tablets; failure of the Quality Unit to reject products not meeting specifications, to complete Quality Assurance investigations, to expand investigations to other lots and products, to file NDA Field Alerts within timeframes, and to respond to out of specification products on the marketplace. Analytical methods requiring remediation remained in use and approximately [redacted] prescription drug products had no analytical evaluations of impurities on stability. Written procedures were not followed and changes with potential product quality impact were not all reviewed and approved by the Quality Unit. No market action was taken by the Quality Unit for any products on the market at the initiation of the inspection of the inspection despite confirmed out of specification, in-process, finished product and stability results. During the inspection, commitments to recall products were initiated based on inspectional findings. No comprehensive risk assessment or quality evaluation for all products on the market was conducted by the firm's Quality Unit prior to completion of the inspection. No additional systems were covered following the documented Quality System failure."

"Commitments to recall finished products from the marketplace were initiated on 4/09/08 and continued throughout the inspection for such products as Digoxin Tablets, Pentazocine and Nalaxone Hydrochloride Tablets, Carisoprodol/Aspirn/Codeine Phosphate Tablets, Hydrocodone Bitartrate and Homatropine Methlybromide Tablets and Mult-Bets pediatric prescription vitamins. However, there is no assurance of the strength, quality and purity of the approximately [redacted] of other products that remain on the market, all lots remaining in the two distribution centers, and the in-process products that remain at the firm's Little Falls, NJ and Totowa NJ locations. The products were manufactured, tested and released by the same Quality System".

(Reference: Attachment A37)

43. Actavis issues urgent recall notice to valued customers stating:

    "This recall notice has been initiated due to overweight tablets."

    (Reference: Attachment A35)

44. 25 April 2008 FDA and Actavis announce recall on all Digitek Tablets on the market. (Reference: Attachment B41)

45. On June 11 2008 Sigurdur Olafsson, now Deputy CEO, Actavis Group, CEO Actavis, Inc. issued response to FDA Form 483's generated during the 8 March to 20 May 2008 FDA inspection. He acknowledges most of the observations, but disagrees when he does not believe them to be correct. The following statement best captures his sentiment:

    "It is quite fair to say, as we related to our April 2008 letter, that Actavis Totowa prides itself in maintenance of cGMP compliance by virtue of comprehensive and robust quality systems. Thus we were surprised and chagrined, as the last inspection developed, by our failure to have secured the compliance we had sought and committed to establish for Actavis Totowa."

    (Reference: Attachment A61)

46. UDL Internal Investigation Record from March 2008 indicates "…one complaint for Digitek 125 mcg (#08-038) reported that the customer observed that the tablets appear smaller than usual and that her heart started racing". This observation was made in March before any recall announcement. (Reference: Attachment A36)

47. Actavis Investigation #08-060 for Digoxin Tablets 0.125 mg Lot # 80228A1, 1 April 2008. Overweight tablets were found during packaging. Preliminary investigation showed a 5000 count bottle had 17 out of 30 tablets above 120 mg. Put on hold pending QA investigation. (Reference: Attachment A39)

48. Actavis contracts Health Hazard Evaluation which is issued 18 April 2008. Conclusions:

    "Double thick tablets could lead to digitalis toxicity; Can result in death. Thin tablets may cause congestive heart failure and arrhythmia."

    (Reference: Attachment A40)

49. Mylan acknowledges Pharmacist identifying double thick products in market place (Reference: Attachment A58)

50. Actavis begins receiving a substantial number of complaints regarding Digitek (Reference: Attachment A59)

51. The management team responsible for all Operations, Administration and Quality at Amide was essentially the same for Amide since 1989 until 2008. These individuals include:

    a. Chandu Patel-President (~1984 to April 2003, Father of Divya Patel died, referenced within Divya C. Patel deposition 30 April 2010)
    b. Divya Patel- President (1995 to April 2008, took over as President when father died in April 2003, reference deposition 30 April 2010)
    c. Ashok Nigayale- R&D (June 1993 to January 2008, reference deposition 31 March 2010)
    d. Jasmine Shah- Quality and Regulatory Affairs (1988 to August 2008 reference deposition 26 March 2010)
    e. Dan Bitler- Quality Assurance (1995 to 23 May 2008 reference deposition 22 January 2010)

52. Ashok Nigalaye leaves company January 2008 (Reference: p. 29 deposition 31 March 2010)

53. Divya Patel leaves company April 2008 (Reference: p. 190 deposition of Divya Patel)

54. 27 April 2008 Mylan Chuck Koon in an e-mail to Hal Korman expresses concerns about Actavis problems with compliance being know “Well over a year ago.” Also talks about how to get out of 10 year contract. (Reference: Attachment A56)

55. Sigurdur Oli Olafsson and Mark Keatley e-mail exchange on 2 May 2008, begins discussion of financial impact of problems associated with Digoxin production at Little Falls. Points include:

    a. What is FY 2008 revenue and gross margin for product?
    b. Any deaths or injuries alleged against us?
    c. Are we covered by insurance vs. product/process liability and Mylan liability?
    d. Estimated recall cost only for this product
    e. Need Digitek answers asap

    (Reference: Attachment A50)

56. Jeffrey Rope and Grudrun Eyjolfsdottir e-mail exchange on 3 May 2008 communicates equipment upgrades and concerns related to Digitek production which include:

a. Have recommended purchase of 3-4 new PTK [tablet] presses with compaction force weight control and automatic reject.
b. Digoxin presses will be fitted with Kramer de-duster to protect operators from Digoxin tablet dust during packaging.
c. "In my view it is totally unacceptable that our people cannot read English operating procedures and batch records."

Jeffrey Rope confirms manufacturing people cannot read English and therefore cannot read operating procedures and batch records.

(Reference: Attachment A51)

57. In an e-mail dated 6 May 2008 from Mike Adams, Executive Director QA Compliance Mylan Pharmaceuticals to a large number of staff members, the following points were made with respect to the status of Digitek recall:

a. "Actavis is setting up a process for consumers to obtain a blood test (through Quest)"
b. "Actavis has addressed over 2,500 medical questions since April 25 2008"
c. Total call volume to Stericycle since recall notice 128,768

(Reference: Attachment A59)

58. Actavis indicates plan to purchase new tableting equipment with weight controls (Reference: Plaintiff's Exhibit 140)

59. Dan Bitler leaves company 23 May 2008 (Reference: p. 16 deposition 22 January 2010)

60. Jasmine Shah leaves company August 2008 (Reference: p.8 deposition 26 March 2010)

61. 1 August 2008 Actavis and FDA announce voluntary recall of all products manufactured at Little Fall, New Jersey facility. (Reference: Attachment B43)

62. 14 November 2008 Complaint for Permanent Injunction United States of America vs. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe

(Reference: Attachment B44)

63. 23 December 2008 Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe.

(Reference: Attachment B45)

Appendix D:

Failure of the Quality System: Examples at Amide/Actavis

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
1983 EIR form Little Falls New Jersey Inspection (A1)	1. No stability data to support 2 year expiry		1. Lack of reconciliation of number of tablet cores after compression 2. Unauthorized changes in batch record			1. Incomplete label inventory
20 April 1989 Voluntary Agreement	1. Inadequate general procedures 2. No procedure to periodically review written procedures 3. Insufficient numbers of staff to support operations 4. No Material Review Board 5. Laboratory audits not performed 6. Inadequate general GMP training	1. Inadequate technical training it laboratory, 2. Laboratory personnel unable to properly use instrumentation 3. No methods validations 4. Inadequate data review	1. Inadequate production procedures 2. Problems with Blend Uniformity 3. Products failing in-process testing			
1989-1990 EIR Little Falls, NJ (A2)	1. Failure to submit periodic reports on ANDA products 2. Inadequate general procedures 3. No procedure to periodically review written procedures 4. Insufficient numbers of staff to support operations 5. No Material Review Board 6. Laboratory Audits not performed	1. Insufficient methods 2. Inadequate technical training it laboratory, 3. Laboratory personnel unable to properly use instrumentation 4. No methods validations 5. Inadequate data review	1. Reuse of parchment paper for drying separate batches of product	1. Inadequate incubator control		

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1992 Consent Decree (A3)	1. Records required by GMPs and internal SOPs not being kept 2. Personnel don't possess background, education, training and experience 3. Inadequate number of staff	1. Methods no validated 2. Methods not scientifically valid 3. Laboratory procedures not followed 4. Data not being recorded at time of testing 5. Laboratory personnel not properly trained				
1994 EIR Little Falls, NJ (A4)	1. QA does not always approve initiation of manufacturing processes. 2. QA releasing batches without review of supporting data packages 3. QA releasing product before process validation reports were written 4. Inadequate manufacturing investigations: No root cause analysis 5. Manufacturing progresses without QA signatures at necessary steps during manufacturing (batch record signatures).	1. Methods not properly validated 2. Failing test results not investigated 3. Modification of sample methods and testing into compliance 4. Modified sample preparation at will 5. Testing methods for single product did not take different tablet weights into account for analysis and calculation of results	1. Outside contractor not following procedures and altering them at will. 2. Problems discovered with process validation were ignored 3. Cleaning validation studies not conducted 4. Batch records modified at will during course of production 5. Batch records sometimes "blank forms" filled in during production 6. Not aware of requirement for three batches as part of process validation 7. Failures during process	1. Use of old and worn out tablet press tooling 2. No maintenance or calibration scheduled for manufacturing equipment including tablet presses and tooling. 3. Inadequate control and sign out of manufacturing tooling.	1. Use of raw materials from different vendors, not all meeting required specifications 2. Use of material form unapproved vendors in violation of internal SOPs 3. Inadequate controls regarding release of raw material from quarantine	

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			validation were ignored. 8. No assurance of blend uniformity is attained during process validation and finished product manufacturing 9. Particle size distribution problems leading to non-uniform blends 10. Modification of acceptance criteria during course of process validation 11. Product released to market before process validation reports were written 12. Lumps reported in final blend leading to overweight and broken tablets 13. Black specs found in blend and tablets, yet no investigations conducted nor procedure in place to address 14. Incomplete cleaning validations			
Form 483 Issued 16 March 1995		1. Improper technique during Digoxin dissolution testing				

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(A5)						
1997 EIR Little Falls, NJ (A6)	1. Failure to follow SOPs for in-process sampling 2. Change control not followed to reflect changes in specifications 3. QA didn't sign off on production records at time of production. 4. Adverse Drug Event reports sent to FDA not recorded or tracked. 5. Customer complaint SOP is inadequate 6. Product related investigations SOP is inadequate: equipment involved not documented; no timeframe for completing 7. Alternate manufacturing SOP inadequate: Planned Deviations and Emergency Deviations ill defined 8. Product reject SOP inadequate	1. Inadequate methods validation: lack of impurity profile testing for numerous products including Digoxin 2. Failure to identify and test for impurities 3. Use of integrators does not allow review of audit trails. 4. No stability data exist to support reference standard expiration: Digoxin and others 5. Inadequate calibration and maintenance procedures for HPLC systems 6. Reinjection of solutions and reanalysis of chromatograms without justification, explanation or investigation 7. Problems with carryover not properly addressed 8. Data in notebooks don't reflect actual procedures performed at the bench by chemists: steps like sonication and filtration not written down	1. Inadequate cleaning validation 2. No process validation to support tablet hardness specification 3. Tablet presses operated outside validated range for speed 4. No tablet press speed range tested during process validations 5. No stability data to support tablet drying operations 6. Modification of production steps without justification or supporting studies 7. Manufacturing investigations not conducted when products found to not meet specifications 8. Re-work procedures not approved in advance nor documented when performed.	1. No SOP for water sampling and testing for water used in manufacturing. 2. No environmental monitoring devices to detect humidity and temperature in: Raw material, in-process storage area, coating rooms, temporary staging hallways		

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Form 483 issued from 29 October to 29 November 2001 (A11)			1. No assurance that all short weight/thin tablets were rejected from batch 2. There is no rework procedure written for the tablet inspection of drums 3. No assurance that all tablet press stations are checked during start up tests and thus produce tablets of proper weight and thickness			
2006 EIR Little Falls, NJ (A18)	1. No assurance that Quality Unit can be relied upon to fulfill it responsibilities to assure that all drug products released to the marketplace meet the requirements for identity, strength, quality and purity that they purport to have. 2. Batches failing to meet specification released into interstate commerce without full investigations 3. All laboratory data no included with batch records 4. No assurance that Quality Assurance can detect discrepancies in reports for which they are	1. Laboratory records are deficient in that they do not include a complete record of all data obtained during testing: sample preparations, errors; low yields not documented 2. SOP for OOS investigations not always followed by laboratory personnel: results improperly invalidated 3. Laboratory notebooks not properly maintained; over-writes; changes made after notebook signed off 4. Input to and output from laboratory computers are not	1. Manufacturing deviations not always documented 2. Cleaning validations not properly performed; equipment might not be clean 3. No assurance that in-process materials meet specifications: proper testing of samples is not performed. 4. Products failing to meet in-process testing specifications are not rejected. 5. No assurance line operators can detect and document out of specification tablets.	1. Equipment qualifications are not adequate and do not insure the equipment will work as designed and used. 2. Equipment re-qualifications not performed to current industry standards 3. Written	1. Rejected in-process materials are not identified an controlled under an quarantine system to prevent their use in manufacturing or processing for which they are suitable: batches not labeled for reject stored with other materials in the work in	

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	responsible 5. Written stability testing program not followed; bulk product only-no testing on fished products in all package configurations 6. QA inspectors not taking action to reject out of specification products which they discovered during manufacturing 7. QA SOPs such as "Routine Tablet Press Overchecks" not being followed	checked for accuracy 5. Cleaning methods not properly validated	6. Master production records are deficient and do not include complete sampling procedures. 7. Sampling of in-process materials not specifically defined in writing.	procedures are not established and followed for the cleaning and maintenance of equipment including utensils; duct take used for repairs	progress warehouse 2. Written procedures are not followed for the receipt and storage of components: components stored and located in unexpected areas; location not listed on inventory cards 3. Failure to handle and store components at all times in a manner to prevent contamination; weighing room not cleaned between uses	
2006 EIR 4 Taft Road, Little Falls, NJ (A23)		1. Deviations from written specifications, test procedures and laboratory mechanisms are not justified:	1. Inadequate cleaning validation studies: not test for cleaning agent; no recovery studies			

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		2. Original values which were failures ignored and retests conducted several times (testing into compliance) 3. Investigations not conducted 4. Validation studies conduct on the fly- filter studies 5. Unknown peaks not indentified 6. No assurance that methods are appropriate for use due to repeated testing without invalidating original out of specification data obtained during method validations. 7. Failures during methods validation were not addressed.				
2007 EIR Little Falls, NJ (A29)	1. NDA Field Alert was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in an application	1. Long gaps exist between testing of samples which initially failed specifications 2. Written stability program not followed: product not tested at 36 month stability point	1. SOP for investigation of OOS results not followed as written: investigations not closed within 30 days, interim reports not generated for on going investigations.			
2008 EIR Little Falls, NJ (A38)-	1. The responsibilities and procedures applicable to the quality control unit are not fully					

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Quality System Review Only (A38)	followed 2. Drug products failing to meet established specifications and quality control criteria are not rejected. 3. There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed 4. Determinations of conformance to appropriate written specifications for acceptance are deficient for in-process materials 5. Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identify, strength, quality and purity. 6. Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did					

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	not extend to other batches of the same drug product and other drug products that may been associated with the specific failure or discrepancy 7. An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application. 8. Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications 9. Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance. 10. Changes to written procedures are not reviewed and approved by the quality control unit. 11. Drug product production and					

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	control records are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed					
2008 EIR Elizabeth, NJ (A43)			1. Flow in in-process materials through the building is not designed to prevent contamination			
14 Nov 2008 Complaint of Permanent Injunction	1. Quality Assurance failed to initiate an investigation when there where multiple complaints for the same lot or confirmed contamination complaints 2. Quality Assurance personnel failed to follow written procedures 3. Quality Assurance failed to ensure all data was reviewed 4. Quality Assurance failed to ensure all laboratory deviations were resolved prior to release of drug into commercial distribution 5. Quality Assurance failed to have adequate written procedures	1. Failure to investigate unexplained OOS testing results 2. Failure to keep complete laboratory records of all testing data 3. Failed to verify the suitability of all testing methods under actual conditions of use 4. Laboratory deviated without written justification, from its own written specifications, test procedures and laboratory mechanisms 5. Laboratory had not established the accuracy, specificity, and	1. Failure to establish control procedures to validate the performance of manufacturing processes 2. Failure to record and justify deviations from its written production and process control procedures 3. Failure to examine and test examples samples to ensure that in-process materials confirm to specifications			

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	6. Failure to document and investigate failure of drug batches to meet specifications 7. Failure to reject drug products failing to meet established standards and specifications and any other relevant quality control criteria.	reproducibility of the test methods that it employed 6. Failure to have laboratory controls sufficient to ensure components, in-process materials, and finished drug products have appropriate standards of identity, strength quality, an purity and conform to their written specifications				